

HIGH DOSE INHALED CORTICOSTEROID THERAPY IN NON  
ASTHMATIC CHRONIC AIRFLOW OBSTRUCTION:

A COMPARATIVE STUDY OF THE SHORT TERM  
EFFECT ON LUNG FUNCTION, SYMPTOMS,  
BRONCHIAL RESPONSIVENESS, AND  
PERIPHERAL NEUTROPHIL FUNCTION, AND  
OBSERVATIONS ON THE LONG TERM ROLE OF  
SUCH TREATMENT.

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## ***ABSTRACT.***

This thesis has investigated and compared the short term effect of treatment with 750 micrograms and 1500 micrograms twice daily of inhaled beclomethasone dipropionate (BDP), and oral prednisolone 40 mg per day, on lung function and quality of life in 105 patients with non asthmatic chronic airflow obstruction. The role of physiological and clinical features in determining the response to treatment in individuals has been investigated, and the systemic and local side effects of therapy have been studied. The effect of treatment on peripheral neutrophil function has been investigated in a subgroup of patients, and observations on decline in FEV1 in a separate cohort of patients are presented.

After three weeks treatment both doses of BDP produced equivalent, small but statistically significant improvements in FEV1, FVC, and mean PEF, compared to that seen with placebo. Individual patients demonstrated a response, defined on the changes seen in physiological variables, to active treatment more commonly than with placebo. Bronchial responsiveness to inhaled histamine was unaltered by treatment for three weeks with inhaled BDP. Quality of life and subjective measures of dyspnea showed marked baseline variability, but treatment with BDP significantly improved dyspnea and patient's 'mastery' over the disease. Oral prednisolone did not improve lung function or subjective measures further. A response to active treatment in individual patients was more common in those with more severe physiological impairment. Formal discriminant analysis was unsuccessful in predicting response to treatment in individual patients.

No significant deleterious effect of treatment with inhaled BDP or oral prednisolone on global respiratory muscle strength was detected. Treatment with BDP caused detectable adrenal suppression, which was dose related, for 750 micrograms twice daily, approximately one tenth that seen with oral prednisolone 40 mg per day, and for 1500 micrograms twice daily, one quarter. Local side effects were more common after inhaled therapy compared with



placebo, but affected only a minority of patients.

Peripheral neutrophil activation was suppressed by treatment with inhaled BDP, and a fall sputum albumin concentration suggested a reduction in bronchial tree inflammation with treatment.

The uncontrolled observational study failed to confirm previously reported associations between decline in FEV<sub>1</sub>, and bronchial hyperresponsiveness, and reversibility of FEV<sub>1</sub> to bronchodilators. The short term response to corticosteroids did not correlate with subsequent decline in FEV<sub>1</sub>. In 32 patients who started regular inhaled BDP midway through the observation period the decline in FEV<sub>1</sub> fell significantly, by over one half, over the remaining period of observation. These observations question the role of short term steroid trials, and suggest a disease retarding effect of inhaled BDP in these patients with non asthmatic chronic airflow obstruction.

This thesis has been composed and written by myself.

The studies reported herein have for the most part been carried out by myself. The work reported in chapters 11 to 13 was carried out in collaboration with others, although the design of these studies and the analysis was performed by myself. Cortisol assays were performed by the Department of Clinical Chemistry at East Birmingham Hospital. The assays of neutrophil function were carried out by scientific officers, that for sputum and serum albumin concentrations by myself. The data for the final chapter were collected with the considerable help of Mr GA Wieland, who shared the task of assessing patients with myself.

The data included in this thesis have not been submitted elsewhere for any degree, diploma or professional qualification, and has not been published save in abstract form.

David C Weir

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## Abbreviations used in the text.

95 %CI	-	The 95 percent confidence interval for the mean.
BDP	-	Beclomethasone dipropionate.
COPD	-	Chronic obstructive pulmonary disease. Used interchangeably with chronic airflow obstruction.
cpm	-	Counts per minute
FEV1	-	Forced expiratory volume in one second.
FRC	-	Functional residual capacity.
FVC	-	Forced vital capacity.
g/l	-	Grammes per litre
IgE	-	Immunoglobulin E
kPa	-	Kilo Pascals
mcg or mg	-	Micrograms.
mls or ml	-	Millilitre(s)
mmol	-	Millimole
nmol/l	-	Nanomole per litre
PD20	-	Provocative dose of histamine causing a 20% fall from baseline in FEV1.
PD20 USDW	-	Provocative dose of nebulised distilled water causing a 20% fall from baseline in FEV1.
PEF	-	Peak expiratory flow rate.
Pemax	-	Maximal expiratory mouth pressure.
Pimax	-	Maximal inspiratory mouth pressure.
PMN	-	Polymorphonuclear leucocytes. Used interchangeably with neutrophils.
RV	-	Residual volume.
SEM	-	Standard error of the mean.
TLC	-	Total lung capacity.
ul	-	Microlitres
umol	-	Micromoles.
VAS	-	Visual analogue scale

## **1. INTRODUCTION.**

### **1.1 HISTORICAL PERSPECTIVE.**

The effect of airflow obstruction on health appears to have been described initially by Plato . He wrote

" When the lung whose office is to dispense the breath to the body, is blocked by rheums, and affords no clear passages, the breath fails to reach some parts, and causes them to putrefy for lack of refreshment..."(1).

Plato obviously realised the deleterious effects that respiratory failure can have on the function of other organs such as the heart and kidney.

Badham was the first to introduce the word "bronchitis", and he gave a more detailed description of the clinical condition(2). It was Laennec who seems to have realised, over 150 years ago, that chronic airflow obstruction could be the result of more than one pathological process(3). He determined that airflow obstruction could occur because of narrowing of the bronchi, or because of loss of surrounding tissue support, or perhaps more commonly because of a combination of both.

He wrote

" In emphysema the air makes its escape from the air cells much slower than in a healthy state of the organ. This seems to indicate either more difficult communication between air contained in the air cells and that of the bronchi, or else diminished elasticity of the air cells themselves. Perhaps both causes conspire to produce the effect in question."

However interest in chronic airflow obstruction was poor until

late in the twentieth century. In 1923 Collis highlighted the importance of chronic bronchitis as a cause of morbidity and mortality, and the lack of interest in the condition by physicians generally(4).

"The trite observation that familiarity breeds contempt is essentially true with regard to the outlook on chronic bronchitis: those afflicted are inclined to accept the complaint as inevitable, as something troublesome but not serious. Those called upon to treat it do not find it sufficiently interesting to study it closely. At a hospital it tends to be disregarded with an out-patient mixture yet....records in England and Wales show that when mortality and morbidity are taken together, bronchitis is the most important of all diseases and further.... it is at the same time a most preventable disease"

It was not until the Medical Research Council created a committee to coordinate research into chronic bronchitis in 1953, following the excess deaths associated with the December 1952 London fog, that our understanding of the epidemiology, pathophysiology and treatment of the condition improved.

## **1.2 EPIDEMIOLOGY.**

Studies have convincingly shown that cigarette smoking is the most important cause of chronic airflow obstruction and emphysema. A dose response relationship was seen between mortality from chronic bronchitis (or chronic airflow obstruction) and the amount of cigarettes smoked in a longitudinal study of 40,000 British doctors(5). However there is an individual susceptibility to these agents, as only a minority of smokers develop airflow obstruction and or emphysema. Outdoor air pollution, at least that seen in the 1960's, has been causally associated with morbidity and mortality from chronic airflow obstruction, and

recently occupational exposure to dusts has been recognised as an important causative factor(6). Indoor air pollution is a major cause of chronic bronchitis in countries where open fires indoor are common(7), and evidence suggests that childhood respiratory illness predisposes to problems in adult life(8). Such causes explain the occurrence of chronic airflow obstruction in non smokers, a fact obvious in times when cigarette smoking was much less common(4).

Although clinically the impression is that the morbidity and mortality from chronic airflow obstruction and emphysema are falling, figures from the U.S.A show that in the age group 55-85 years, morbidity as measured by office visits has increased slowly over the period 1979-1985(9). The increase is probably due to the aging of the birth cohort born 1910-1949, who have had the greatest cohort cigarette exposure, and who are only now presenting with symptomatic smoking related chronic airflow obstruction.

In the late 1970's a population based study in Tecumseh, U.S.A. showed a fairly high prevalence of airways obstruction, defined as an FEV1 less than 65% of the predicted value. Ten to fifteen percent of males aged 45-64 years, and approximately 5% of females fulfilled these criteria(10). It might be expected that only a proportion of subjects with airflow obstruction would have symptoms attributable to the physiological abnormality, but in the U.K. two recent general practice based studies have shown symptoms of cough, and dyspnoea on performing activities of daily living in 5-20% of the population studied(11,12), suggesting the prevalence of respiratory symptoms and airways obstruction in a community may be similar, and confirming the significant morbidity from this cause.

Mortality from chronic bronchitis, emphysema and asthma on the other hand, has halved over the period 1969 to 1985 in all age groups, and in both sexes(13). A further decrease in mortality would be expected in the future if the recent downward trend in smoking is continued. The proportion of men smoking fell from 52% to 36% from 1970 to 1984, and from 41% to 32% in females over the same period. However the number of women smoking in the 20 to 34 year age group has increased by 10% in the years 1980 to 1984, a statistic

which suggests that chronic bronchitis and emphysema will continue to cause significant amounts of illness in the population. Indeed in 1977/78 10% of all working days lost due to sickness were attributed to these diseases(14), and in 1985 Williams and Nicholl suggested sixty thousand patients in England and Wales should be receiving long term treatment with oxygen because of the effects of severe chronic airflow obstruction(15). Their figures suggest this subgroup of patients with hypoxic disease probably represents about 3% of individuals with an FEV1 less than 70% of the predicted value, so the potential demand on health service resources from this condition is considerable.

### **1.3 DEFINITIONS.**

Chronic airflow obstruction is a term which literally describes the physical effects of a number of disease processes on the flow volume characteristics of the lung. Because different disease processes may have varying prognostic implications there has been much semantic discussion about exact definitions of the disease entities which make up the syndrome of chronic airflow obstruction. Two Ciba symposia(16,17), and articles in learned journals reflect this(18,19,20).

The three major disease processes which cause chronic airflow obstruction are asthma, emphysema and chronic (obstructive) bronchitis. Chronic bronchitis has been defined as a cough productive of sputum on most days for at least three consecutive months for two consecutive years(21). The condition is not invariably associated with chronic airflow obstruction, and epidemiological evidence suggests that chronic bronchitis and chronic airflow obstruction should be considered as separate entities rather than as different manifestations of the same disease(22).



Pathologically chronic bronchitis is characterised by hyperplasia of the mucous glands in the larger ( >2mm diameter) airways(23), and an accompanying inflammatory cell infiltrate(24). In those patients with chronic bronchitis and chronic airflow obstruction the site of the obstruction to airflow is in the small airways, less than 2 mm in diameter(25). These smaller airways show evidence of progressive inflammatory cell infiltration, leading to fibrosis and thickening of the airway walls(26).

Strictly emphysema is defined in pathological terms, although it may be detected with reasonable accuracy in life by indirect means, such as measurement of single breath carbon monoxide gas transfer (TLCO), or the volume corrected diffusing capacity (KCO)(27) or by CT scanning of the lungs(28). Pathologically it has been defined as

"a condition of the lung characterised by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis"(29).

Emphysema is usually accompanied by chronic airflow obstruction although the exact cause of this is still unclear(30). The relative importance of loss of elastic recoil and reduction in peribronchiolar support due to the emphysematous process, and the thickening and narrowing of the peripheral airway lumen by the chronic inflammation seen to the reduction in airflow is still debated.

The precise definition of asthma has been elusive, but Scadding's attempt seems as good as any,

"a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways(31)".

Difficulties arise however in deciding what degree of variation constitutes asthma, and whether variation should be expressed in absolute or percentage terms. Only recently has the pathological changes in the airways of patients with asthma been investigated. Epithelial denudation, and infiltration of the mucosa



and lamina propria of large airways by eosinophils and lymphocytes have been described(32,33).

In any one patient the contribution of each disease process to symptoms and the abnormal physiology seen will vary and may be of only academic significance. However it appears that prognosis, and by implication response to treatment, depends upon the underlying cause of the airflow obstruction. In Tucson a longitudinal population based study has shown that patients with asthma, for whom effective treatment in the form of inhaled corticosteroids is available(34,35), have a more benign disease(36). In practical terms therefore it appears important to identify those patients with asthma.

In 1986 The American Thoracic Society issued a definition of asthma, and chronic obstructive pulmonary disease (chronic airflow obstruction) which included symptoms, response to treatment and histology(37). The major differences between asthma and chronic airflow obstruction from other causes was the paroxysmal and variable nature of both the symptoms and the physiological abnormalities. Such a definition is not of major clinical use as some patients labelled as asthmatic have persisting airflow obstruction, with little spontaneous or drug induced related reversibility in airflow obstruction(38), whereas many patients with chronic airflow obstruction who smoke and have physiological evidence of emphysema show varying but clinically relevant reversibility in response to drugs. The similarity between asthma and chronic airflow obstruction has led some workers to postulate that they are but two manifestations of the same disease process(39).

Because of difficulties in definition of each disease, for the purposes of this study a practical, clinically relevant definition of asthma was adopted. Only patients with chronic airflow obstruction who the physician felt were not obviously clinically asthmatic, and therefore in whom the benefits of treatment with oral or inhaled corticosteroids could not be assumed, were recruited. Asthma as the underlying cause of the disease was favoured if there was a history of childhood respiratory problems, or if the patient reported wheezing and breathlessness on exposure to specific allergens, or marked

variability in their symptoms except with exercise and infections. A lack of a fixed element to the airflow obstruction also suggested asthma as the underlying diagnosis. Conversely a history of heavy cigarette consumption, persistent and constant symptoms, and a classical history of chronic winter bronchitis implied a non asthmatic cause to the disease.

Although firm physiological criteria to try to define asthmatics were not used, and physicians will differ slightly in their definition of asthma, the patients recruited were intended to reflect clinical practice, and to be representative of those patients in whom a therapeutic trial of corticosteroids has been recommended(40,41). Such a definition of chronic airflow obstruction will include patients whose physiological abnormality is the result of a number of different causes, but it is simple and obviates the need for more complex investigations, such as CT scanning or histological examination of biopsy material, which would be necessary if more precise accurate definition was required.

#### **1.4. TREATMENT OF CHRONIC AIRFLOW OBSTRUCTION.**

Patients with chronic airflow obstruction generally complain of dyspnoea, cough and sputum production as their major symptoms. Physiologically, abnormalities of expiratory flow, ie reduced FEV1\FVC ratio, and reduced carbon monoxide gas transfer are apparent. The aim of treatment is to relieve symptoms, improve measures of airflow and if possible prevent progression of disease. In smokers the cornerstone of management is smoking cessation, although the success of physicians achieving this is poor, varying from 5-10% with simple advice in outpatients attending chest clinics, to only 25% at twelve months following intervention in well

motivated smokers, recruited from the community, receiving pharmacological and psychological help(42,43). Quitting smoking will remove the cause of the disease and will result in a reduction in the rate of loss of lung function, as measured by FEV1, to normal levels(44,45). This probably occurs within 5 years , and in younger patients an improvement in lung function may occur as a consequence of stopping smoking alone(45).

Optimal use of both oral and inhaled bronchodilators will maximise airflow, and will to a varying extent relieve symptoms of dyspnoea. Both beta adrenergic and anti-cholinergic drugs are effective in producing bronchodilation in most patients with chronic airflow obstruction. In some patients subjective benefit may be obtained from these drugs with little change in objective measures of airflow obstruction, reflecting the complex relationship between symptoms and objective measures of lung function in this group of patients.

Oral methylxanthines are commonly used as second line drugs, and are effective, but require monitoring of serum concentrations to prevent toxicity problems, and to optimise effect(46). The use of oral corticosteroids will be considered in greater detail later.

Antibiotics are certainly effective during infective exacerbations of the condition(47), but there is no evidence that continuous long term antibiotic therapy has any beneficial effect on disease progression(48). The role of mucolytics is controversial in the UK, although recent evidence suggests that they produce symptomatic benefit in the majority of patients(49). Formal exercise programs are believed to be effective in some patients(50), and inspiratory muscle training appears to improve exercise tolerance in patients with fairly severe airflow obstruction(51).

Relief of breathlessness may be achieved by drugs acting entirely on the neural mechanisms responsible for this sensation, eg diazepam, dihydrocodeine. These drugs have no detectable effect upon objective measures of airflow obstruction but may improve exercise tolerance and breathlessness in 'pink puffers'(52), although

anecdotally such treatment is rarely clinically useful. Available treatments are not always successful, especially in the relief of breathlessness, and this has led some to perform dubious surgery in an attempt to obtain relief. Carotid body resection has been reported to dramatically relieve dyspnoea, but at the expense of decreased minute ventilation and worsening of arterial blood gases(53).

During infective exacerbations of the condition controlled oxygen therapy, and diuretics are used for worsening cor pulmonale, and antibiotics for infection. Oral corticosteroids are commonly used during acute exacerbations, although the evidence that they are effective is based on one study only. This showed small differences between treated and placebo groups in lung function during the first 72 hours of admission. The clinical significance of these changes was not clear, there were no differences in mortality, and the study did not consider if treatment actually shortened hospital admission(54).

In terms of improving survival in patients with chronic airflow obstruction, very few treatments have been shown to have any effect. Long term oxygen therapy will prolong survival in the subgroup of patients with severe airflow obstruction who are hypoxaemic at rest(55,56). In addition two retrospective studies from Dutch workers in Groningen have suggested that moderate doses of oral prednisolone may slow down disease progression and improve survival(57,58). If these findings are confirmed in prospective studies the advice that corticosteroids should only be prescribed to patients with chronic airflow obstruction who show objective improvement in a short term 'trial of steroids' may turn out to be misguided(40,41).

## **1.5. CORTICOSTEROIDS IN THE TREATMENT OF CHRONIC AIRFLOW OBSTRUCTION.**

The efficacy of corticosteroids in the treatment of chronic airflow obstruction has usually been assessed in short term studies over two to four weeks. Many papers purporting to assess this short term effect of corticosteroids in chronic airflow obstruction have been published, and have been reviewed by other authors(59,60,61). The majority are concerned with the use of oral corticosteroids(62-92), very few studies have investigated the role of inhaled corticosteroids in chronic airflow obstruction. Only two published reports adequately address the longer term effect of corticosteroids in chronic airflow obstruction, and these will be reviewed later(57,58).

### **1.5.1. Short term treatment with oral corticosteroids in chronic airflow obstruction.**

Comparison of the results reached by the various authors is extremely difficult because of differences between studies in fundamental areas such as trial design, patients studied, and often in the method chosen to analyse the data collected. When assessing the conclusions reached by different authors it is therefore important to assess all the factors inherent in the trial which may influence the results obtained. As Stoller et al have indicated although the majority of published trials seem to show little benefit from treatment with oral corticosteroids, the studies with positive results are better designed and statistically the most precise of the trials published(60).

The design of the trial and the use of appropriate controls will have a strong influence upon the ability of the therapeutic trial to detect a treatment effect. From 1951 to 1990 twelve studies used an essentially flawed trial design, in that no placebo control was used(62-73) (listed overleaf in table 1.1.). This makes the conclusions reached by the authors almost impossible to evaluate as no allowance has been made in their analysis of the short term variability in the outcome measures used.

Table 1.1. Published uncontrolled studies of the effect of oral corticosteroids on chronic airflow obstruction

Author and Year	No of Pts	Drug	Dose	Time	Entry Criteria	Outcome Measures	Analysis	Results	Mean FEV1
Lukas <sup>62</sup> 1951	13	acth cort	var	?	?	fvc mbc		descriptive	
Bickerman <sup>63</sup> 1955	50	pred	var	var	?	svc mbc	categ	86%	?
Franklin <sup>64</sup> 1958	58	pred cort	40mg 160mg	var var	clin	fev1	categ + change	25/55	42% pred
Lorriman <sup>65</sup> 1959	6	pred	10 to 20mg	3-42	?	fev1 tlco	categ ?	1/6	0.89
Cullen <sup>66</sup> 1960	14	pred	30 to 60mg	7	?	fev1 fvc, mbc	categ ?	0/14	1.21
Clifton <sup>67</sup> 1962	28	pred	30mg	7	clin	fev1 fvc	categ > 20%	15/21	
Pecora <sup>68</sup> 1963	7	meprd	40mg	7	clin	fev1 fvc, mbc	categ ?	0/7	?
Freedman <sup>69</sup> 1963	26	pred	var	28	clin	fev1 fvc	both > 20%	neg 5/26	1.04
Fuleihan <sup>70</sup> 1967	10	beta	4mg	21	clin	fev1 fvc	group	pos	?
Klein <sup>71</sup> 1969	18	pred	40mg	14	clin	fev1 fvc	both arbitrary	neg 6/14	?
Lightbody <sup>72</sup> 1978	10	pred	30mg	3	clin	fev1 cycle erg	group	neg	1.28
Nisar <sup>73</sup> 1990	127	pred	30mg	14	fev1/fvc < 60%	fev1	categ 15% + 200ml	27/127	0.92

Drugs- pred=prednisolone, beta=betamethasone, cort=cortisone, meprd=methylprednisolone

Time- duration of trial. Entry criteria- clin=clinical criteria only

Outcome measures- parameters used in assessment of response,

mbc-maximal breathing capacity, cycle erg-cycle ergometry.

Analysis- see text for definitions. Second line refers to categorical analysis criteria.

Results- pos= steroids beneficial or neg= no effect of steroids for group analysis, or numbers (%) responding for categorical analysis.

Mean FEV1 refers to all patients. ? Unclear from paper or data not given.



The remaining studies have all used placebo controls in either a single or double blind trial design. Four studies have used a single blind design(74-77) (table 1.2.), with the placebo treatment period preceding active treatment in all patients. This risks introducing bias in the assessment of drug effect, as the observer is aware of the treatment order but this can be controlled for by using

Table 1.2. Published single blind placebo controlled studies of the effect of oral corticosteroids on chronic airflow obstruction

Author and Year	No of Pts	Drug	Dose	Time	Entry Criteria	Outcome Measures	Analysis	Results	Mean FEV1
Oppenheimer <sup>74</sup> 1968	26	pred	20mg	7	fev1/fvc < 60%	fev1,fvc pef,sGaw rv,tlc	both	neg 0/26	?
Williams <sup>75</sup> 1980	20	pred	30mg	14	clin	fev1,fvc 12mwd	group	pos	0.98
Stokes <sup>76</sup> 1982	31	pred	30mg	14	'severe CAO	fev1,fvc pef	both > 20%	neg 4/31	0.95
Swinburn <sup>77</sup> 1988	20	pred	30mg	14	clin	fev1,fvc SaO2	group	pos	0.86

Drugs- pred=prednisolone, beta=betamethasone, cort=cortisone, meprd=methylprednisolone

Time- duration of trial. Entry criteria- clin=clinical criteria only

Outcome measures- parameters used in assessment of response

sGaw-specific airways conductance, 12mwd-12 minute walking distance, SaO2-capillary oxygen saturation.

Analysis- see text for definitions. Second line refers to categorical analysis criteria.

Results- pos= steroids beneficial or neg= no effect of steroids for group analysis, or numbers (%) responding for categorical analysis.

Mean FEV1 refers to all patients. ? Unclear from paper or data not given.

rigorous predetermined criteria for acceptance of objective measurements. In addition, as little information is available on the time course of response to corticosteroids, such a design avoids the possibility of a carry over effect from the active treatment into the placebo, dummy period.

The remaining fourteen studies have used a double blind placebo controlled format, in twelve papers in a crossover design(79-85,88-90,92,93) in the final two in a parallel group design(87,91) (table 1.3. & 1.4.). Parallel group studies may be confounded by the introduction of bias into the treatment groups recruited. By chance they may not be balanced in terms of factors likely to influence response to treatment which are not specifically controlled for in the entry criteria for the study. This is especially true in smaller studies.

As mentioned above a crossover design suffers from possible carry over effects of active treatment into a subsequent placebo treatment period. As patients are randomly allocated to the order in which treatments are received, this effect may bias results by increasing the number of apparent placebo responses and diminishing the actual difference between placebo and active treatments. This effect can be minimised by appropriate washout periods between treatments. However there is a dearth of data on the duration of effect of treatment after it has been withdrawn. Our own analysis in a similar patient group suggests that treatment effects may be seen up to six weeks after treatment is withdrawn(78). A similar duration of effect of corticosteroids occurs in asthmatic patients(79). At the very least therefore a washout period of three weeks would appear advisable to ensure carry over effects will be negligible.

In the studies in tables 1.3. and 1.4. washout periods varied from zero(79,83,93), seven days(89), or 14 days(84,85,90,91), to 42 days(80). Hence in all but one of these studies a possible carry over effect of active corticosteroid treatment may have occurred. Only one of these studies specifically commented on a possible carry over effect, but the ability of the study to detect such an effect was low because of the small number of patients studied(92).



Table 1.3. Published double blind placebo controlled studies of the effect of oral corticosteroids on chronic airflow obstruction showing no effect of corticosteroids

Author and Year	No of Pts	Drug	Dose	Time	Entry Criteria	Outcome Measures	Analysis	Results	Mean FEV1
Beerel <sup>80</sup> 1963	10	pred	30to 60mg	14	fev1 < 1.0	fev1,fvc rv,tlc	both ?	neg 2/10	0.56
Morgan <sup>81</sup> 1964	7	beta	3.6mg	28	clin	fev1,fvc rv,tlc	group	neg	1.22
Beerel <sup>82</sup> 1971	23	pred	30to 60mg	56	clin	fev1,fvc tlco abg	group	neg	?
Evans <sup>83</sup> 1974	10	pred	5mg	7	clin	fev1,fvc sGaw	group	neg	1.11
O'Reilly <sup>84</sup> 1982	10	pred	30mg	14	clin	fev1,fvc tlco 12mwd	both, > 10%	neg 3/10	0.81
Strain <sup>85</sup> 1985	13	meprd	32mg	14	fev1/fvc < 60%	fev1,fvc cycle erg	group	neg	1.16
Eliasson <sup>86</sup> 1986	16	pred	40mg	14	fev1 < 60% rev < 15%	fev1,fvc	both, > placebo change	neg 2/16	1.24

Drugs- pred=prednisolone, beta=betamethasone, cort=cortisone, meprd=methylprednisolone

Time- duration of trial. Entry criteria- clin=clinical criteria only

Outcome measures- parameters used in assessment of response

mbc-maximal breathing capacity, abg-arterial blood gases, sGaw-specific airways conductance, 12mwd-12 minute walking distance, cycle erg-cycle ergometry.

Analysis- see text for definitions. Second line refers to categorical analysis criteria.

Results- pos= steroids beneficial or neg= no effect of steroids for group analysis, or numbers (%) responding for categorical analysis.

Mean FEV1 refers to all patients. ? Unclear from paper or data not given.

Table 1.4. Published double blind placebo controlled studies of the effect of oral corticosteroids on chronic airflow obstruction showing a positive effect of corticosteroids

Author and Year	No of Pts	Drug	Dose	Time	Entry Criteria	Outcome Measures	Analysis	Results	Mean FEV1
Hurford <sup>87</sup> 1963	39	pred	30mg	7	clin	fev1,mbc	categ >150mls	4/19	0.86
Shim <sup>88</sup> 1978	24	pred	30mg	7	clin	fev1,fvc	categ >30%	7/24	0.73
Mendella <sup>89</sup> 1982	46	meprd	32mg	14	fev1 < 60 % predicted	fev1	both > 29 %	pos 8/46	1.03
Lam <sup>90</sup> 1983	16	pred	40mg	14	fev1 < 65 % predicted & fev1/fvc < 65 %	fev1,fvc pef 12mwd	group	pos	0.85
Blair <sup>91</sup> 1984	44	meprd	32mg	10	fev1 < 1.15 fev1/fvc < 60 %	fev1,fvc	both > 25 %	pos 8/29	0.74
Mitchell <sup>92</sup> 1984	43	pred	40mg	14	clin	fev1,fvc rv,tlc tlco 12mwd	both > 20 %	pos 14/33	1.02
Mitchell <sup>93</sup> 1986	33	pred	40mg	14	clin	fev1,fvc rv,tlc pef 12mwd	both > 20 %	pos 13/33	1.01

Drugs- pred=prednisolone, beta=betamethasone, cort=cortisone, meprd=methylprednisolone

Time- duration of trial. Entry criteria- clin=clinical criteria only

Outcome measures- parameters used in assessment of response,  
mbc-maximal breathing capacity, 12mwd-12 minute walking distance.

Analysis- see text for definitions. Second line refers to categorical analysis criteria.

Results- pos= steroids beneficial or neg= no effect of steroids for group analysis,  
or numbers (%) responding for categorical analysis.

Mean FEV1 refers to all patients. ? Unclear from paper or data not given.

The method of analysis chosen will also affect the conclusions of the study. Two main methods of analysis have been employed in published papers. Group analysis investigates if treatment produces a statistically significant change in the mean value of the outcome variable studied. Statistically this method of analysis is valid but it may mask responses to treatment in individual patients. Not all patients with a particular disease would be expected to respond to all therapy available to treat that disease, hence concentrating exclusively on such analysis may lead to effective therapy for some patients being discarded. In addition although statistically significant changes may be shown after treatment their magnitude may be such that clinically the improvement gained is trivial.

An alternative approach is to assess the efficacy of treatment by determining the number of patients in whom a particular outcome variable improves by a predetermined clinically relevant amount (categorical analysis). Such an approach has been used in some studies of corticosteroids in chronic airflow obstruction, but is only valid if adequate precautions are taken to allow for natural variability in the outcome measure used, both in the design of the trial and in choosing the degree of change in the variable which will be considered significant in an individual patient. Lack of data on the natural short term variability of many of the outcome variables used until recently(94) made the definition of significant improvement an arbitrary choice, as is reflected in the wide variation quoted in the published papers.

Ideally both methods of analysis should be used, so that valuable information is not lost. Interestingly 4 out of the seven negative double blind studies used a group analysis only(80-82,84), whereas all but two(87,88) of the positive studies used both methods of analysis. Subsequent group analysis of both these negative trials also shows significant effects of corticosteroid(60). Categorical analysis of the positive trials indicates that between 17% and 33% of patients will respond to corticosteroids with an increase in at least one outcome variable by over 20%. Even in the negative trials where categorical analysis has been undertaken between 12.5% to 30% of patients appear to respond to corticosteroids.

The number of patients studied is another factor which determines the sensitivity of a study. If too few patients are studied a statistically non significant result may occur even though a real difference exists. Conversely a large study may detect small absolute differences which are statistically significant, but which clinically are meaningless. Stoller et al(60) show that in studies where a group analysis was used, the three positive studies with the greatest statistical precision(87,88,90) are the three studies with the greatest number of patients recruited, 16, 24 and 39 patients compared to 7,10, and 10 patients in the three negative, less precise studies(80,82,83). The choice of outcome measures will also have an important bearing on the conclusions reached by a study. The parameters chosen may be dictated by the question asked, but the use of at least one objective measure has been advocated, because of the supposed euphoriant effect of oral steroids(41), as Freedman wrote

"the euphoriant effect of prednisolone led to a number of greatly inaccurate subjective statements in patients in whom the FEV1 remained the same or diminished"(69).

The majority of trials since 1963 have placed little weight on subjective improvement, and made scant attempt to quantify this. Indeed only five published studies have related subjective change after treatment with that seen in objective measures used(75,77,83,90,92), most studies making vague comments about symptomatic improvement. Whilst it is clear that potentially dangerous drugs should not be prescribed for purely symptomatic reasons, the patients assessment should arguably play a large part in guiding treatment.

A wide variety of outcome measures have been used in the published literature, as can be seen from the tables. This reflects the fact that the most clinically relevant objective tests are not clear. The results of the five studies which correlated change in objective measures of lung function with formally measured symptomatic change should provide data which could answer this question. However their results are not in agreement. Williams and McGavin

found changes in FVC correlated most strongly with subjective change, measured by a visual analogue scale(75), but Swinburn et al(77), O'Reilly et al(83) and Lam et al(90) found no correlation between changes in FVC and changes in their subjective measures. Mitchell et al found the strongest correlation between changes in 12 minute walking distance and a general well being scale, although again changes in FVC correlated reasonably well with changes in subjective measures(92). In a study specifically designed to detect euphoric effects of steroids Swinburn et al did find an improvement in a number of psychological measures which preceded any change in the objective parameters, suggesting a euphoriant effect of the drug and emphasising both types of assessment need to be an integral part of such trials(77).

Most studies have used at least one of the spirometric variables, FEV1 or FVC, as an outcome measure. Mitchell et al comment however that serial peak expiratory flow(PEF) measurements are a more sensitive test(93). Of 13 patients showing an improvement in serial PEF of at least 20%, less than half showed an associated improvement in FEV1. The increased number of measurements made with serial PEF recordings was thought to decrease the signal to noise ratio and hence increase the sensitivity of the measurement. Their results are borne out by our own earlier study(95). When changes in FEV1 and/or FVC and/or domiciliary serial PEF measurements were used to define response to treatment, a response occurred in all three variables in only 11 % of responses, to two variables in 26% of responses and in one variable only in nearly two thirds of all the responses seen. Multiple outcome variables therefore appear to increase the likelihood of detecting a treatment effect.

A case can also be made for including functional measures in the assessment of corticosteroid therapy. Measurement of exercise capacity appears to provide extra, slightly different information, as improvement in exercise performance has been shown to occur without changes in spirometry(96). The extra information gained requires a large investment in time terms, and others have shown that change in 12 minute walking distance correlates with change in

serial PEF(92), FVC(75), and carbon monoxide gas transfer(83). A simpler objective measure may therefore suffice, but the ideal objective measure or measures is far from clear.

Differences in the drug used in the assessment of response to corticosteroids may alter the conclusions reached, but it is more likely that differences in the dose used explain some of the differences in response rate. In acute asthma Webb suggests that a dose of prednisolone of 0.6mg/kg/day, equivalent to approximately 40mg per day, is optimal for producing physiological improvement(97). Whether stable patients with non asthmatic chronic airflow obstruction require similar doses to ensure maximum response is unclear. Only nine of the studies tabulated above however, used a daily dose of 40mg per day of prednisolone or equivalent, although many more used 30 mg prednisolone per day. Studies which employed lower doses of corticosteroid have always produced negative results.

The duration of treatment given will also influence the response to treatment. Hurford et al noted that response to prednisolone may be delayed, with the maximum response not appearing until after 14 days treatment in 2 of 6 patients studied(87). Blair and Light found significant improvements in lung function at 10 days but not after 5 days treatment with methylprednisolone(91). Webb et al showed response to oral prednisolone in a group of predominantly asthmatic patients occurred by the eleventh day of treatment(98), and our own analysis suggests that maximum response will not be reached in up to 20% of patients by fourteen days(78). Hence of the trials listed in tables 2-4, five gave treatment for inadequate periods(74,81,87,88,91) and only two gave treatment for long enough periods to ensure all responders to treatment were identified(80,81).

Finally differences in patient selection will also explain differing conclusions. Response to corticosteroids appears to be related to reversibility to bronchodilators(88,89,91), serum eosinophilia(88) and skin test reactivity(71). Hence differing entry criteria will inevitably lead to differences in the population studied,



and partially explain response rates. Eliasson and colleagues(85) comment that steroid response appears to be inversely related to initial level of airflow obstruction is borne out by comparing the mean baseline FEV1 of the trials in table 3 (negative) with table 4 (positive). Negative trials have an average baseline FEV1 of 1.07 litres, compared to 0.75 litres in trials with positive conclusions.

In summary the evidence suggests oral corticosteroids are effective treatment in stable chronic airflow obstruction. The better designed, statistically more precise trials reach positive conclusions. Nevertheless the studies still have methodological flaws and the conclusion may be more applicable to patients with severe airflow obstruction.

#### **1.5.2. Short term treatment with inhaled corticosteroids in chronic airflow obstruction.**

A number of studies have shown the benefit of inhaled corticosteroids in patients with asthma(34,35,99). It would be expected that patients with non asthmatic chronic airflow obstruction, a proportion of whom show benefit from treatment with oral corticosteroids, would respond to the inhaled form of the drug. Only four studies have investigated this however(95,100-102).

The earliest published paper compared oral prednisolone with inhaled betamethasone valerate and placebo(100). Patients were defined on clinical and physiological grounds, with symptoms of chronic bronchitis, and spirometric evidence of airways obstruction. Two groups of 18 patients were studied, one group as inpatients, the other in an outpatient setting. Outpatients received 10 days treatment with placebo, followed by a modest dose of betamethasone valerate (800ug per day) for a further 10 days, and finally oral prednisolone 30 mg per day. This part of the trial was a single blind, sequential, double dummy design. Two patients did not receive the full dose of oral prednisolone.

The inpatients received 7 -10 days of a placebo inhaler, followed by inhaled betamethasone valerate 800 ug per day for 7-10

days, and finally oral prednisolone 30mg per day for one week. Half of this group received the final treatment as an outpatient, and two patients were withdrawn because of dyspepsia.

Only six of the 36 patients showed a response to oral prednisolone, although response was not formally defined. Of these six, the 4 inpatients showed a similar response to the inhaled drug, whereas the outpatients showed little improvement after betamethasone valerate. This was attributed to drug delivery problems. The authors felt that supervision of aerosol inhalation technique improved drug delivery and explained the differences in the results. Although this study suggested inhaled corticosteroids would be effective in this group of patients, the poor adherence to a fixed trial design in the inpatients, the low dose of inhaled drug used, and the short time for which it was given make firm conclusions impossible.

Shim and Williams studied twelve patients with chronic airflow obstruction who had previously shown a response to oral prednisolone(101). Whilst continuing a maintenance dose of 5mg per day of oral prednisolone, patients received either prednisolone 30mg per day, or a low dose of inhaled beclomethasone dipropionate 160mcg per day. A double blind crossover design was used, with a 14 day washout period which would not reliably exclude a carry over effect(78). Delivery of the drug was optimised by the improvised use of a Ziploc freezer bag as a reservoir spacing device. In a group analysis both oral prednisolone and inhaled beclomethasone dipropionate improved FEV1 significantly. Five of the 12 patients showed an increase in FEV1 of over 20% after inhaled beclomethasone dipropionate, all showed a similar increase after oral prednisolone. The magnitude of the increase after inhaled beclomethasone dipropionate in FEV1 was approximately 50% of that seen after oral prednisolone. The results suggest that inhaled beclomethasone dipropionate is an effective treatment in a proportion of patients with chronic airflow obstruction who respond to oral prednisolone. However the results are not generally applicable to all patients with chronic airflow obstruction, and must be interpreted with caution as some patients had been taking inhaled



beclomethasone dipropionate in unspecified doses for up to 2 weeks prior to the study, and the effect of maintenance low dose oral prednisolone is not clear.

In a small study of subjects with clinically defined chronic airflow obstruction 22 patients received inhaled and oral corticosteroids in a single blind sequential study which did not appear to use a double dummy technique(102). Patients were treated with placebo inhalers and tablets for two weeks , followed by placebo tablets and inhaled beclomethasone dipropionate 1500ug per day for a further two weeks, and finally oral prednisolone 30 mg per day alone for two weeks. A group analysis did not show any significant effect of either active drug in this small group of patients, but five patients showed an increase of at least 20% over placebo in serial PEF measurements and FEV1, or FVC after inhaled beclomethasone dipropionate. A further mean improvement of 15% occurred in these patients after oral prednisolone. Again the conclusion that inhaled beclomethasone dipropionate is at least partially effective in patients showing a response to oral corticosteroids must be tentative in view of the inadequacies of trial design, and the loose entry criteria adopted.

Our own study comparing oral prednisolone 40mg per day, inhaled beclomethasone dipropionate 1500ug per day, and placebo is the largest such study in the literature(95). One hundred and twenty seven adults entered the study, 107 completed the protocol. The trial was a double blind, crossover study using a double dummy technique. Patients received an inhaler and tablets for each 2 week treatment phase, which was followed by a two week washout period before the next randomised treatment was started. Tablets and inhalers contained active drug or placebo as appropriate. Only a categorical analysis was undertaken, using criteria similar to those used in previous studies to determine response. An improvement in absolute values of FEV1, and/or FVC recorded on the final day of treatment, and/or the mean PEF over the final seven days of the treatment period of at least 20% over baseline values was considered a response to treatment.

Despite the two week washout period the analysis detected a statistically significant order effect in the response to placebo. That is responses to placebo were detected more frequently if placebo had been preceded by an active treatment phase. This suggested a carry over effect of active treatment of at least 14 days, and our subsequent analysis showed an effect of active treatment 28 days after the treatment had been withdrawn in some patients(78). This complicated the analysis of the study, but we were able to show a statistically significant effect of both oral prednisolone, and inhaled beclomethasone over placebo. Approximately 20% of patients showed a response to inhaled beclomethasone, and nearly twice this number to oral prednisolone.

The use of three outcome measures to define response probably explains the apparent increase in the response rate to oral prednisolone compared to previous trials. The response rate to inhaled beclomethasone may have been further increased if a spacing device had been used to deliver the drug. Such devices increase delivery of aerosolised drug by up to 100%(103), and even with repeated instruction the correct use of metered dose inhalers alone by patients is poor(104). The study lacked formal subjective assessment in all patients. However the first 83 patients completed visual analogue scales for five symptoms, and had 12 minute walking distance measured. These showed a statistically significant improvement in 12 minute walking distance in the responders to active treatment, and an improvement in visual analogue scores which was not statistically significant, possibly due to the large variance of these measures(105).

The conclusion was that inhaled beclomethasone is about half as effective in producing physiological response in patients with chronic airflow obstruction compared to oral prednisolone. This reduced effectiveness of inhaled corticosteroids may be explained by a reduced dose of corticosteroid delivered to the airways and it is possible that a higher dose of inhaled beclomethasone would be more effective. This hypothesis was the underlying rationale for the majority of the current study.

### **1.5.3. Long term studies of corticosteroids in chronic airflow obstruction.**

There are no studies of adequate design which have addressed the long term effect of oral or inhaled corticosteroids in chronic airflow obstruction. Three uncontrolled studies have been published, and the results from these suggest that moderate doses of oral prednisolone may slow down disease progression and improve mortality (57,58,106).

The earliest report was of an open study of the effects of injections of 40mg methylprednisolone given every 8 to 14 days for up to a year(106). Only 20% of patients with chronic airflow obstruction showed an improvement in peak expiratory flow after treatment, although the clinical result was thought to be acceptable in 7 of 11 patients.

The initial report from the Groningen group concerned the effect of treatment with oral prednisolone on decline in FEV1 and mortality in 79 patients with severe chronic airflow obstruction, that is an FEV1 at the start of the 18 year study of less than 1.0 litre(57). This analysis identified three patterns of decline in FEV1 over the follow up period. One pattern was a linear decrease in FEV1, a second a significant increase followed by a decrease, and a third showed no change in FEV1 with time. Survival in the three groups was significantly different, the five year survival being 75%, 100% and 86% respectively in the three groups, and at 14 years 20%, 58% and 40%. In the group showing a linear decline in FEV1 prednisolone in a dose of at least 7.5 mg per day was taken on average for 20% of the observation period, for 56% of the follow up period in those showing an increase followed by a decrease in FEV1 and 90% of the time in patients showing no change in the FEV1 over the observation period, strongly suggesting a disease slowing effect of oral prednisolone. This group also demonstrated a strong correlation between the time of reduction in dose of prednisolone to less than 7.5mg per day, and subsequent decline in FEV1. When the dose of oral prednisolone was reduced below this level, the FEV1 always began to fall, but often only after a time interval of between 6

to 32 months.

This retrospective study provides good evidence, as survival data over a long follow up period that oral prednisolone can influence the course of the disease in patients with chronic airflow obstruction. The data on decline in FEV1 need to be interpreted with caution because of the uncontrolled nature of the study, although each of the three groups was comparable in terms of possible confounding factors, eg; age, initial FEV1 level, reversibility to bronchodilators.

In a second report a similar analysis was conducted on patients with less severe chronic airflow obstruction, that is with an initial FEV1 greater than 1.2 litres(58). This study identified four patterns of decline in FEV1 over 14 to 20 years. Again a correlation between the time the daily dose of prednisolone was reduced below 10mg, and the beginning of a decline in FEV1 was noted. Treatment with at least 10 mg per day oral prednisolone was followed by an increase in FEV1 over time, but often not until 6 to 24 months of continuous treatment. The authors comment that in patients with chronic airflow obstruction the effect of oral corticosteroids appears to take a longer time to become apparent than in patients with asthma. This suggestion implies that most published studies on the use of corticosteroids in chronic airflow obstruction have failed to identify all patients in whom this treatment would be beneficial.

## **1.6. BRONCHIAL HYPERRESPONSIVENESS IN CHRONIC AIRFLOW OBSTRUCTION.**

Bronchial hyperresponsiveness is defined as an increase in the magnitude and ease of airway narrowing to a variety of non allergic stimuli(107). In the long term studies from the Groningen group bronchial hyperresponsiveness to inhaled histamine was shown to be an independent predictor of decline in FEV<sub>1</sub>(108). This supported the hypothesis from the Dutch workers of the 1960's who suggested that bronchial hyperresponsiveness was, in addition to an allergic constitution the major pathogenetic mechanism involved in the development of both asthma and chronic airflow obstruction, and that these two diseases could be regarded as two aspects of the same basic process(39).

A diagnosis of asthma is often taken as being synonymous with bronchial hyperresponsiveness. Bronchial hyperresponsiveness in asthma can be demonstrated to variety of inhaled agents, some of which act directly on bronchial smooth muscle, eg metacholine, histamine, and others that act indirectly, eg hyperventilation of cold air, exercise, hypotonic or hypertonic aerosols. The presence and severity of bronchial hyperresponsiveness in asthma correlates reasonably well with disease activity, as measured by diurnal variation in PEF(109), and treatment requirements(110), suggesting it is part of the underlying abnormality in asthma. The degree of bronchial hyperresponsiveness also correlates with the number and activation of inflammatory cells in bronchoalveolar lavage fluid recovered from asthmatics(111,112). Treatment with corticosteroids improves bronchial responsiveness and asthmatic symptoms, and also decreases inflammatory infiltration of the airway epithelium in asthma(113,114,115), strongly supporting the contention that bronchial hyperresponsiveness is a cardinal feature of asthma.

In patients with chronic airflow obstruction bronchial hyperresponsiveness can also be demonstrated but it shows different characteristics to that seen in asthma. The dose response curve in non asthmatics shows a plateau not present in asthmatics(107), the degree of bronchial hyperresponsiveness seen for a given reduction in FEV<sub>1</sub> is less(116), and there is a correlation between the degree of



airflow obstruction and the bronchial hyperresponsiveness seen(117,118). It would also appear that patients with chronic airflow obstruction show a different pattern of sensitivity to inhaled agents than patients with asthma. Asthmatics have a higher incidence of bronchial hyperresponsiveness to metacholine, histamine, propranolol, sulphur dioxide and cold air(119), and it has been suggested that bronchoconstriction to the inhalation of a hypotonic aerosol (fog) is specific to asthma(120).

These differences from bronchial hyperresponsiveness seen in asthmatics have led to debate about whether the mechanisms underlying bronchial hyperresponsiveness are the same in each disease group, and to the relevance of the 'Dutch' hypothesis in the pathogenesis of smoking related airflow obstruction(121).

In asthma bronchial hyperresponsiveness develops before the development of a late asthmatic response in patients challenged with various occupational agents(122). This change in bronchial hyperresponsiveness occurred before any change in airway calibre, and the degree of bronchial hyperresponsiveness seen at 3 hours post challenge correlated with the severity of the late fall in FEV1. These findings suggest that bronchial hyperresponsiveness in asthma primarily reflects events in the bronchial wall which lead to bronchoconstriction, and is independent of airway narrowing.

Airway hyperresponsiveness in patients with non asthmatic chronic airflow obstruction however may reflect other causes. Narrowing and distortion of airways may alter the smooth muscle mechanics in the bronchial wall, so that a given stimulus to muscle contraction causes a greater degree of airway narrowing. Such changes in muscle mechanics could be due to hypertrophy of muscle or secondary to a decrease in the force resisting contraction because of loss of peribronchiolar attachments. There is evidence for both in some patients with chronic bronchitis(123,124). Additionally any thickening of the airway wall would result in exaggerated narrowing of the airway lumen for a given degree of smooth muscle contraction. Both mucosal inflammation and fibrosis would have this effect(26). Finally the deposition and retention of the inhaled agent may change

with increasing airway obstruction, and this may amplify the effect of the agent.

These three putative mechanisms may explain bronchial hyperresponsiveness in non asthmatic chronic airflow obstruction to a large degree. Certainly the relationship between FEV1 and bronchial responsiveness seen in most studies is likely to be due to such causes. In Yan et al's study overall a correlation between bronchial hyperresponsiveness (PC20) and FEV1:FVC ratio was seen(125). However when patients with relatively normal FEV1 values were considered the relationship between PC20 histamine and FEV1:FVC ratio disappeared. It is clear however that smokers with chronic bronchitis and 'normal' FEV1 values do show bronchial hyperresponsiveness of a minor degree, but certainly less than that seen in asthmatics(126), suggesting other factors aside from morphological changes to the airway contribute to bronchial hyperresponsiveness in these patients. In a physiopathological study workers from Vancouver showed significant independent influences of airway calibre, airway inflammation, and cigarette smoking on PC20 to histamine or metacholine(127). It would seem therefore that bronchial hyperresponsiveness in non asthmatic chronic airflow obstruction may reflect to a certain degree inflammatory processes in the airway wall, as in asthma, but primarily the geometric effects of the disease process.

Some studies have shown a relationship between accelerated decline in FEV1 and bronchial hyperresponsiveness(108,128,129), suggesting bronchial hyperresponsiveness is important in pathogenesis. However in two of these studies bronchial responsiveness was measured at the end of the period of observation, and as a reduction in FEV1 can itself lead to bronchial hyperresponsiveness due to geometric factors alone, separating cause and effect and the relevance of bronchial hyperresponsiveness in these studies is difficult.

As inflammation seems inextricably linked to bronchial hyperresponsiveness in asthma, one possible way of studying the importance of this phenomenon in chronic airflow obstruction is to



look at the effects of interventions designed to reduce airway inflammation on bronchial responsiveness and decline in lung function.

Stopping smoking decreases bronchial inflammation(130), and slows the rate of decline in FEV1 to normal(44). Hence if bronchial hyperresponsiveness reflects active inflammation this should improve. No studies have measured bronchial hyperresponsiveness before and after stopping smoking. However in a study of changes in bronchial responsiveness to inhaled histamine and FEV1 over 4 years, the authors concluded that the lack of change in bronchial hyperresponsiveness to histamine despite a reduction in decline in FEV1 in ex smokers supported the importance of geometric factors rather than active inflammation as the major determinant of bronchial responsiveness(131).

Corticosteroids also reduce inflammation and bronchial hyperresponsiveness in asthma(113,115). One study has examined the effect of corticosteroids on bronchial hyperresponsiveness in patients with chronic bronchitis(132). The patients selected for this study were smokers with moderate to severe bronchial hyperresponsiveness to inhaled histamine, but with no evidence of airway obstruction (FEV1 greater than 70% predicted). Over a twelve week period inhaled budesonide at a dose of 800ug per day produced no significant change in bronchial hyperresponsiveness or in lung function parameters in the 8 patients receiving treatment compared to the ten receiving placebo. Whether a higher dose of inhaled steroid or a longer period of treatment would produce any change is still unclear. Three other studies used higher doses of inhaled budesonide and also failed to show any effect on bronchial hyperresponsiveness. Pride et al studied 14 middle-aged smokers, known to have an accelerated decline in FEV1, treated with inhaled budesonide at a dose of 1200mcg per day over 12 weeks(133). No change in various lung function parameters, or bronchial responsiveness to histamine was noted. A recently published study showed no effect of 1600mcg per day of inhaled budesonide for eight weeks on bronchial hyperresponsiveness, spirometry or citric acid cough threshold in smokers with chronic airflow obstruction(134). Oral prednisolone at

a dose of 40 mg per day actually worsened bronchial hyperresponsiveness in smokers with mild chronic airflow obstruction, although the change was measured after only 4 days(135). These small studies, not all fully published, tend to suggest that bronchial hyperresponsiveness in patients with non asthmatic chronic airflow obstruction does not improve after measures which improve bronchial hyperresponsiveness in asthmatic patients. This would cast doubt on the 'Dutch' hypothesis and tend to relegate bronchial hyperresponsiveness in these patients to a paraphenomenon. As Postma has suggested however the beneficial effect of corticosteroids on lung function in this group of patients may not become apparent for up to six months, and hence the studies so far reported may be misleading(58).

The differences in the characteristics of bronchial hyperresponsiveness in asthma and chronic airflow obstruction, especially the apparent specificity of a response to cold air hyperpnea(119) and 'fog' inhalation(120) in asthma, have led to the suggestion that bronchial hyperresponsiveness to indirect non sensitising stimuli may identify a group of patients with chronic airflow obstruction who will benefit from corticosteroid treatment(136). No previous study has specifically addressed this question, although from Ramsdale et al's data cold air responsiveness did not seem to correlate with steroid response(118). In a similar study there was a lack of correlation between cold air responsiveness, and the response to a beta agonist or oral prednisolone in 26 patients with clinical chronic obstructive pulmonary disease(137). At the moment the role of bronchial hyperresponsiveness to inhaled agents in predicting response to corticosteroids in patients with chronic airflow obstruction is unclear.

## **1.7. THE ROLE OF THE NEUTROPHIL IN THE PATHOGENESIS OF CHRONIC AIRFLOW OBSTRUCTION AND EMPHYSEMA.**

Although the cellular events which eventually lead to the development of chronic airflow obstruction and emphysema are still unclear, there is a body of evidence that implicates the neutrophil in the pathophysiology of these disease states. Indeed it is generally accepted that the development of emphysema is at least in part due to an elastase imbalance within the lung, the protease-antiprotease theory(138). The major burden of elastase in the lung is thought to derive from the neutrophil, although why only 15% or so of smokers appear to be susceptible to the damaging effects of cigarette smoke is unclear.

Pathological studies have lent support to such suggestions by demonstrating neutrophils in the inflammatory infiltrate of bronchial wall biopsies in patients with chronic airflow obstruction(139). In addition polymorphonuclear leucocytes (PMN) appear to accumulate in the alveolar septa of smokers, the presumptive site of action of their elastase load, although in this small study no correlation was seen between the accumulation of polymorphonuclear leucocytes and the degree of emphysema(140).

Animal studies also implicate the neutrophil in the development of both emphysema, and bronchial hyperresponsiveness. The intratracheal instillation of human neutrophil elastase can induce emphysema in experimental animals(141,142), and neutrophils appear to be essential for the development of bronchial hyperresponsiveness after ozone exposure or allergen challenge in dogs(143,144).

In humans it has been known for a long time that persons with a genetic deficiency of alpha-1-antitrypsin, the major serum inhibitor of neutrophil elastase, are particularly susceptible to the development of emphysema(145). This observation would lend weight to the suggestion that it is this cell type which has the major role in the pathogenesis of this disease.

Normal individuals who smoke also show increased numbers

of neutrophils in bronchoalveolar lavage fluid(146), and in smokers the elastase content of bronchoalveolar lavage fluid correlates with the presence of emphysema defined both radiologically by CT scanning and on physiological criteria(147). In this study a negative correlation between the antielastase activity of bronchoalveolar lavage fluid and emphysema was also seen, as was a positive correlation between the number of neutrophils in bronchoalveolar lavage fluid and the degree of emphysema, adding to the weight of evidence for the protease-antiprotease theory. This group have also shown higher neutrophil counts in the bronchial lavage fluid of patients with chronic bronchitis compared to asymptomatic smokers and normals, and a correlation between bronchial lavage fluid neutrophilia and the degree of airway obstruction(148), suggesting in addition an important role for the neutrophil in the chronic airflow obstruction associated with emphysema.

The mechanism by which neutrophils are attracted to the lung parenchyma from the peripheral circulation is not clear. Cigarette smoke is not chemotactic to neutrophils(149), but cigarette smoke will stimulate the release of potent neutrophil chemotactic factors from alveolar macrophages(150). Similar chemotactic factors can also be found in bronchoalveolar lavage fluid from patients with chronic airflow obstruction(151), and it is likely these are involved in recruitment of neutrophils to the lung. It is possible that the release of such factors also explains the observation of increased polymorphonuclear leucocyte activation in the peripheral blood of cigarette smokers(152), and patients with chronic bronchitis and emphysema(153). Indeed the production of the superoxide anion by neutrophils isolated from the peripheral blood of patients with chronic airflow obstruction correlates with the degree of bronchial hyperresponsiveness in the patients. This suggests a role for these cells in the pathogenesis of both conditions(154).

Although there is strong evidence supporting a pivotal role of the neutrophil in the pathogenesis of chronic airflow obstruction and emphysema, there is little information on the effects of treatment on neutrophil function. Oral corticosteroids can reduce neutrophil activation both in vivo and in vitro(155,156) in normal subjects, and

inhaled budesonide has been shown to reduce some functions of alveolar macrophages in smokers(157), but there is no data on the effect of inhaled corticosteroids on neutrophil function in patients. As inhaled corticosteroid improves lung function in patients with chronic airflow obstruction(95), and low doses of oral prednisolone slow disease progression in this disease(57), it would be interesting to determine the effect of treatment with such drugs on peripheral neutrophil function in patients with chronic airflow obstruction. Especially as the peripheral white cell count is a predictor of decline in lung function in subjects with chronic airflow obstruction(158).

## **2. GENERAL AIMS.**

The aims of the studies which form this thesis were to further investigate the role of oral and inhaled corticosteroids in chronic airflow obstruction, and to investigate cellular mechanisms which may underlie response to such treatment. In addition one part of the thesis documented the change in lung function in a group of patients with chronic airflow obstruction and related the decline in lung function to a number of factors, including treatment with corticosteroids.

The specific aims of the main study were:

1. To compare treatment with placebo, and inhaled beclomethasone at doses of 1500mcg and 3000mcg per day in producing subjective and objective improvement in patients with chronic airflow obstruction not due to asthma.
2. To assess the additional effect of adding oral prednisolone 40mg daily to the above treatment in producing subjective and objective improvement in patients with chronic airflow obstruction not due to asthma.
3. To assess the safety of the above treatment regimes, determined by local oropharyngeal effects, and adrenal suppression.
4. To determine the effects of treatment as outlined above with inhaled beclomethasone and oral prednisolone on bronchial hyperresponsiveness to inhaled histamine in patients with chronic airflow obstruction, and to relate in individual patients changes in bronchial hyperresponsiveness and response to treatment.
5. To determine the effects of treatment as outlined above with inhaled beclomethasone and oral prednisolone on global respiratory muscle strength, measured as maximal inspiratory and expiratory mouth pressures.
6. To examine the role of bronchial responsiveness to ultrasonically nebulised distilled water in predicting response to corticosteroids in these patients.



7. To investigate the relationship between subjective response measured by a quality of life instrument and physiological response defined objectively.

8. To investigate the effect of inhaled beclomethasone and oral prednisolone on peripheral neutrophil activation and chemotaxis, and lung inflammation in a subgroup of patients.

In a second study the change in lung function in a cohort of patients who completed a trial assessing steroid responsiveness between 1983 to 1986 has been documented, and changes seen in individual patients related to smoking, bronchial hyperresponsiveness, the starting FEV1, response to treatment in the original trial, and treatment with oral and inhaled corticosteroids during the observation period. This study was an uncontrolled observational study.



### **3. METHODS.**

#### **3.1. PATIENT SELECTION.**

One hundred and five patients were recruited from NHS Chest Clinics at Solihull Hospital, the Birmingham Chest Clinic, and the East Birmingham Hospital. All six consultant chest physicians working in these hospitals were circulated with details of the trial, its aims and the patient selection criteria. All were requested to refer new patients who fulfilled the criteria to myself for assessment and possible inclusion in the trial. As the trial was designed to reflect a clinical problem patients were recruited on the basis of relevant clinical criteria.

The inclusion criteria were:

1. Male or female patients aged 18 years or over.
2. Chronic airflow obstruction defined as an FEV1/FVC ratio less than 65% and an FEV1 of less than 70% of the predicted value.
3. Symptoms for at least 5 years, beginning during adult life.

Exclusion criteria adopted were;

1. A past or present diagnosis of asthma, made by a consultant physician.
2. Treatment with inhaled or oral corticosteroids in the previous 3 months.
3. An infective exacerbation of their disease (acute on chronic bronchitis) resolving within the 4 weeks prior to recruitment.
4. A history of poorly controlled concomitant disease eg; diabetes mellitus, active peptic ulcer disease, uncontrolled congestive heart failure and untreated pulmonary tuberculosis.
5. Pregnancy or lactation
6. Anybody unable to comply with the protocol due to physical or mental disability (eg; blindness, illiteracy, language difficulties).

Reversibility of the airflow obstruction to bronchodilators was

not included in the criteria because of the relationship between reversibility and the starting FEV<sub>1</sub>(159), which makes the interpretation of apparent reversibility to FEV<sub>1</sub> in patients with low starting FEV<sub>1</sub>'s extremely difficult. A diagnosis of asthma was made at the time of the initial assessment, and patients excluded from the study, if they had a history of variability in symptoms except in association with infections, and if they reported acute attacks of wheezing and breathlessness, a history of chronic respiratory symptoms in childhood, or a deterioration in symptoms following exposure to a specific allergen.

### **3.2. TRIAL DESIGN.**

Because of work showing a carry over effect of corticosteroids of up to 6 weeks(78), the design of the trial was single blind with three, 3 week sequential treatment periods. The treatment periods were preceded by a baseline period of 14 to 21 days during which time bronchodilator therapy was rationalised and optimised, on the results of reversibility tests, and the various baseline investigations performed. For the final week of the baseline period, and throughout the remainder of the trial bronchodilator treatment was continued unchanged.

At the end of the baseline period the patients were randomly allocated one of four possible treatment regimes over the ensuing nine weeks, that is a parallel group design was used. The randomization was blind to both the investigator and the patients. In all groups the first treatment period consisted of placebo inhalers and tablets.

For the second treatment period the patients received either inhaled beclomethasone dipropionate 750 mcg b.d. plus placebo tablets, or inhaled beclomethasone 1500 mcg b.d. plus placebo tablets. The inhaled drug was delivered by two identical inhalers and patients were instructed to take 3 puffs from each inhaler twice daily. Each puff of active treatment delivered 250 mcg per puff of beclomethasone. Eight placebo tablets were prescribed per day, to be taken in the morning after breakfast.

For the final treatment phase, the inhaled therapy allocated during the second treatment phase was continued unchanged, but two thirds of the patients in each BDP dosage group received 40 mg per day oral prednisolone in addition. The remaining 1/3 of each BDP dosage group continued treatment with inhaled beclomethasone and placebo tablets for the final treatment phase.

The patients attended the laboratory on three occasions during the baseline period for pretreatment assessments to be made, ie day -21 (start of baseline), day -7 (mid-way through baseline period) and day 0 (start of the placebo treatment). They were then assessed on the final day of each treatment period, ie; day 21 (end of placebo treatment), day 42 (end of inhaled BDP treatment), and day 63 (end of third treatment phase). Finally they were seen 4 weeks after the end of treatment during which time they continued their usual bronchodilator therapy.

The design employed a double dummy technique. All placebo inhalers and active inhalers were identical and placebo and prednisolone tablets appeared identical. Inhalers were taken via a volumatic spacing device (Allen & Hanburys Ltd, Greenford Middlesex). Patients were instructed at each attendance on how to take inhalers via this device. In addition both written and verbal instructions were given to each patient at each attendance on the dose of each medication to be taken. They were instructed to take 3 puffs twice daily from each inhaler via the volumatic spacing device, and 8 study tablets in the morning after breakfast.

The first three patients followed an identical protocol in a pilot study, but are included in the final analysis.

A schematic representation of the trial design is shown in figure 3.1..

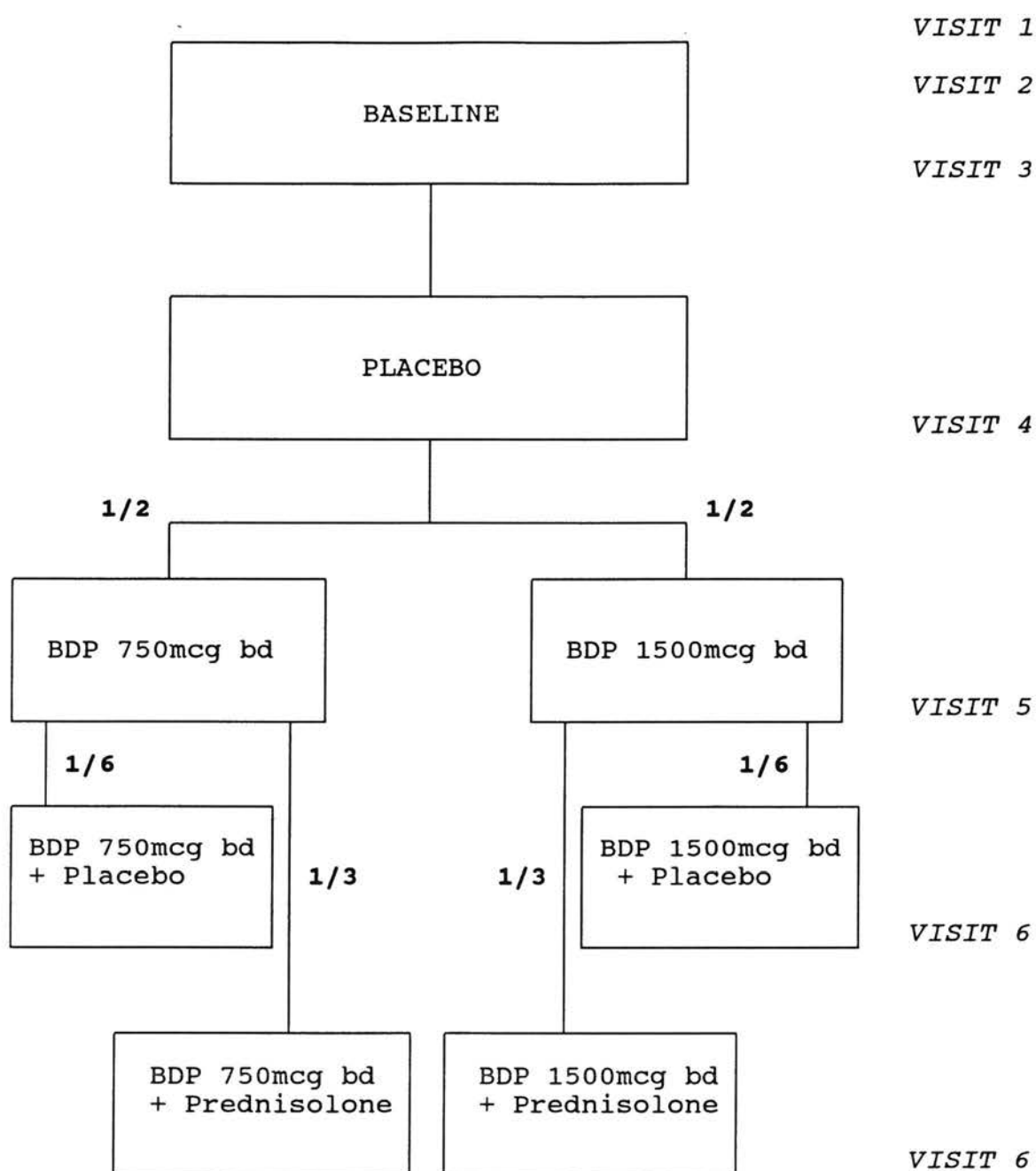


Figure 3.1. Schematic representation of the trial design. Each phase of the trial was 3 weeks long, with assessments on the final day of each treatment phase. The proportion of patients following each pathway is shown in bold type.

### **3.3. WITHDRAWAL CRITERIA.**

Patients were withdrawn from the study for the following reasons.

1. At the patients request because of unwillingness to continue with the trial.
2. Development of significant side effects attributed to treatment
3. Inability to follow protocol
4. Any patient requiring treatment with oral corticosteroids because of an exacerbation of their disease, that is an increase in breathlessness, with or without purulent sputum, accompanied by a fall in PEF or spirometric indices.
5. The development of any serious concomitant disease.

### **3.4. MEASUREMENTS.**

#### **3.4.1. Lung Function.**

All lung function measurements were performed after 20 minutes rest and patients were instructed to refrain from inhaled bronchodilators for 6 hours before the measurements and not to take any oral bronchodilators in the previous 24 hours. All lung function and biochemical tests were performed at the same time of the day, with a tolerance of  $\pm 1$  hour, at all visits.

#### *Spirometry.*

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured on a dry wedge spirometer. This measurement was performed at every visit. The highest value of at least 3 attempts was recorded and used for future analysis, providing the highest two readings of FEV1 were within 50 ml or 5% of each other. Baseline FEV1 and FVC were taken as the mean of the three measurements on the three baseline visits before any treatment.

Patients were seen in three geographically distinct locations (Birmingham Chest Clinic, Solihull Hospital and East Birmingham Hospital) and a different dry wedge spirometer (Vitalograph) was used at each site. However measurements in individual patients were performed on the same dry wedge spirometer throughout the trial. Each spirometer was regularly checked and calibrated, and measurement of FEV1 and FVC of the author were within 5% on each of the three machines used.

#### *Carbon Monoxide Gas Transfer.*

The diffusing capacity of carbon monoxide for the lung (DLCO) was measured by the standardized single breath technique(160). At each site a Morgan Transfer Test module was

used. The best of three measurements made over a 20 minute period was recorded, providing the top two measurements of the DLCO were within 10%. The diffusion coefficient (KCO), ie the diffusing capacity per unit lung volume, and the single breath alveolar volume (VA) were also calculated. The analyzers were calibrated routinely prior to any testing using a test gas and room air. The breath hold time utilized was the maximum the patient could tolerate up to 9 seconds, and the vital capacity employed was at least 70% of that obtained from a slow vital capacity maneuver on a dry wedge spirometer.

This measurement was performed twice during the baseline period, and at each of the three post treatment visits.

#### *Static Lung Volumes.*

Static lung volumes were measured by a closed circuit helium dilution technique on one occasion during the baseline period. Re-breathing was continued for a maximum of 20 minutes or until the helium concentration changed by less than 0.03% over 1 minute. The test was repeated if for any reason it was felt that the result was technically unsatisfactory. Total lung capacity, vital capacity, functional residual capacity, residual volume were all calculated from the readings obtained and the result of slow vital capacity maneuver following the test.

#### *Reversibility of FEV1 and FVC.*

The reversibility of FEV1 and FVC to bronchodilators was measured during the baseline period and also at the end of each treatment period. During the baseline period all patients had reversibility to 200 mcg of Salbutamol and 72 mcg of Ipratropium Bromide measured on different days. The drug was administered via a Volumatic spacing device (Allen & Hanburys Ltd, Greenford, UK)



by the investigator and the response measured 20 minutes later.

In patients with an FEV1 greater than 0.75 litres the reversibility test was performed after the measurement of bronchial responsiveness to inhaled histamine. To eliminate any possible effect of prior bronchoconstriction upon the response to inhaled bronchodilator, the drug was only administered after the FEV1 had returned to the pre-histamine test level or after 30 minutes had elapsed since the end of the test of bronchial responsiveness. The reversibility of FEV1 and FVC was calculated with respect to the pre-histamine FEV1 and FVC.

At the post treatment visits patients were randomised to have reversibility to either Salbutamol or Ipratropium Bromide measured.

Reversibility to FEV1 was expressed in four ways;

(a) as absolute change (ml) from prebronchodilator value (absolute),

postbronchodilator FEV1 - prebronchodilator FEV1

(b) as a percentage of the initial prebronchodilator value (% initial),

$$\frac{\text{postbronchodilator FEV1} - \text{prebronchodilator FEV1}}{\text{prebronchodilator FEV1}} \times 100\%$$

(c) as a percentage of the predicted FEV1 (% predicted),

$$\frac{\text{postbronchodilator FEV1} - \text{prebronchodilator FEV1}}{\text{predicted FEV1}} \times 100\%$$

(d) as a percentage of the 'possible' reversibility (% possible), ie

$$\frac{\text{postbronchodilator FEV1} - \text{prebronchodilator FEV1}}{\text{predicted FEV1} - \text{prebronchodilator FEV1}} \times 100\%$$

### **3.4.2. Bronchial responsiveness to inhaled histamine.**

Bronchial responsiveness to inhaled histamine was measured by two different methods during the baseline period on separate days. The method of Cockcroft et al(161) was used to determine bronchial hyperresponsiveness on one occasion during the baseline period. On the other occasion, and after each treatment the method of Yan et al(162) was employed.

All patients with an FEV1 greater than 0.75 l had bronchial responsiveness to histamine measured. All tests were performed with the subject seated. After the baseline pre-test FEV1 had been measured the patient inhaled the diluent, either phosphate buffered saline (for the Cockcroft method) or normal saline (for the Yan method), as a control. Providing the FEV1 measured after the control inhalation did not fall by more than 10%, increasing concentrations of histamine were then inhaled until the protocol was complete or the subjects FEV1 had fallen to below 80% of the lower of the pre-test or post diluent value. The patient was then supervised until the FEV1 had returned to within 10% of the pre-test value, or until 30 minutes had elapsed from the end of the bronchial responsiveness test, at which stage a reversibility test was performed.

For both methods the concentration (Cockcroft method), or cumulative dose (Yan method) of histamine which produced a 20% fall in the FEV1 (PC20 & PD20 respectively) was estimated by linear interpolation of a plot of percentage fall in FEV1 against the log dose of histamine, with extrapolation to one doubling dose above the maximum administered. The lower of the pre-test FEV1 and that measured after the control inhalation was used to calculate the percentage fall after each dose of histamine.

#### *Cockcroft Method.*

A Wright nebuliser driven by air at a pre-determined flow rate to produce an output from the nebuliser of 0.14 mg/min of nebulised solution was used. The nebuliser was primed with three millilitres of solution and aerosol delivered to the subject by a loose fitting face mask without intervening tubing. The subject wore a nose

clip and inhaled the aerosol by tidal breathing for two minutes. The FEV1 and FVC were recorded prior to any inhalation as described above. After each inhalation, including the control inhalation of the diluent, phosphate buffered saline, the FEV1 was recorded once, unless technically unsatisfactory, at 30 and 90 seconds and at subsequent 90 second intervals until the value showed no further fall. Inhalations of histamine were given by successive doubling concentrations from 0.03 mg/ml to a maximum of 16 mg/ml.

#### *Yan Method.*

The output of several hand held Devilbis number 40 nebulisers were measured to select five with an output within the range 0.0018 to 0.0042 ml/puff. These were primed with 1 to 1.5 ml of either saline or histamine dissolved in saline in concentrations 0.3, 0.6, 2.5 or 5 g/ml. The FEV1 was measured prior to any inhalations as above, and subsequently four puffs of saline were given as the control inhalation. The FEV1 was measured 60 seconds after the last inhalation, and providing the FEV1 had not fallen by more than 10% of the pre-test value histamine was administered.

One or more puffs were delivered from the nebuliser directly in front of the subjects open mouth, at the beginning of a near maximal inspiration from function<sup>at</sup> residual capacity. The patients were coached in the technique of coordinating inspiration. After each dose from the nebuliser the patient held his breath for 3 seconds.

Histamine was administered according to a fixed regime to achieve accumulative doses of 0.03 to 7.8 mmol.

#### **3.4.3. Bronchial responsiveness to ultrasonically nebulised distilled water.**

Bronchial responsiveness to the inhalation of increasing amounts of ultrasonically nebulised distilled water was determined

on one occasion during the baseline period by a modification of the method of Anderson et al(163). A Mistogen EH147C ultrasonic nebuliser with an air mist module was used to generate the aerosol. The output of this module without the breathing circuit was 3 ml/min with a particle size 3 to 5 microns (manufacturers data). The aerosol generated by the nebuliser was delivered to a 2 way valve (Hans Rudolph, Inc., Kansas City, NO.1500) via short lengths of 1.25 inch diameter corrugated tubing. The expired limb of the two way valve was connected by a further corrugated tubing to a Wrights respirometer, from which the volume of aerosol inhaled by the patient was calculated.

The FEV1 was measured prior to the challenge as described above. As a control the patient breathed 40 l of room air through the circuit without any aerosol being generated. The FEV1 was determined 30 seconds after this procedure. If the FEV1 had fallen by less than 15% of the initial value the challenge continued. The variable output control of the nebuliser was set to its maximum and the patient initially inhaled 10 litres of the nebulised aerosol. Thirty seconds after the end of the inhalation the FEV1 was once again determined. If the FEV1 had fallen by more than 20% the test was terminated. If the FEV1 had fallen by between 10% and 20% a further two aliquots of 10 litres of aerosol were inhaled sequentially and the FEV1 determined 30 seconds after each inhalation, the test terminating if the fall in FEV1 after either aliquot was greater than 20% of the pre challenge value. If the fall in FEV1 after the initial 10 litre aliquot of mist was less than 10% the volumes of aerosol used in subsequent inhalations were 20 litres, 40 litres, 80 litres, 80 litres and 80 litres, until a fall in FEV1 of at least 20% of the higher of the pre-challenge or post-air value had been recorded. The test was stopped after a maximum of 310 litres of aerosol had been inhaled.

After each inhalation the weight of the canister containing the distilled water and the tubing connecting the canister to the two way valve was measured using an electronic scale accurate to 0.1 gram. From the change in the weight of this after each inhalation, the volume of water delivered to the mouth of the patient could be calculated. The dose of water in millilitres delivered to the mouth

which caused a 20% fall in the FEV1 was calculated by linear interpolation of a plot of the percentage fall in FEV1 against the change in weight of the canister and tubing.

Following the challenge the patients received 200 mcg Salbutamol via a volumatic spacing device to reverse the bronchoconstriction induced.

Bronchial responsiveness to ultrasonically nebulised distilled water was not measured in all patients. The equipment required for the test was only available after the trial had commenced. Hence only 75 patients were considered for the test and the test performed in 49 patients in whom the FEV1 was greater than 0.75 litres.

#### **3.4.4. Static Mouth Pressures.**

Maximum inspiratory and expiratory mouth pressures were measured on two occasions during the baseline period and on the final day of each treatment phase. A modification of the method of Black and Hyatt was used(164).

A commercially available mouth piece of a semi-rigid plastic flange type (PK Morgan, Chatham, Kent), was used. This was fitted to a rigid stem incorporating a 3 way tap. The stem was of 20 mm internal diameter and 12 cm in length. A leak hole of diameter 2.5 mm was situated 10 cm from the site of the mouth piece attachment. The stem was connected by a 75 cm length of polythene tubing to an anaeroid pressure transducer (Wika Ltd, Coulsdon, Surrey, UK). The manometer was calibrated regularly using a U tube water filled manometer.

Mouth pressures were measured with the subject in the seated position wearing a nose clip. The flange mouth piece was held in the mouth behind the lips and gripped firmly by the teeth, the operator holding the stem. If necessary the subjects used their hands to hold their lips firmly onto the mouth piece. For a maximum expiratory pressure measurement the subject inspired to total lung

capacity, the operator closed the three way tap and the subject was asked to blow maximally down the tube. All subjects were given verbal encouragement and were able to see the manometer reading. A period of familiarization and learning preceded the definitive measurements on each day mouth pressures were determined. At least one minute rest was allowed between efforts. Only pressures maintained for more than 1 second, judged from a stop watch, were recorded. The measurement was repeated at least 3 times, or until the two highest measurements were within 10% of each other. The highest of the measurements was recorded for further analysis.

For maximal inspiratory pressure measurements, the subject expired to residual volume, the operator closed the three way tap and the subject was asked to inspire maximally. Any measurements where there was a visual or audible leak around the mouth piece were ignored.

#### **3.4.5. Blood tests and smoking status.**

All patients underwent venepuncture on one of the three baseline visits for estimation of haemoglobin concentration, total white cell count, differential white cell count including eosinophil count, serum IgE level, serum alpha 1 antitrypsin level, and serum thiocyanate. Serum IgE and alpha 1 antitrypsin levels were measured in the Regional Immunology Laboratory at East Birmingham Health by a standard nephelometric method.

Exhaled carbon monoxide concentration was measured using a portable analyser (Ecocheck EC50, PK Morgan, Chatham, Kent). Professed smoking status was confirmed using the results of this test and the serum thiocyanate concentration. An exhaled carbon monoxide concentration above 8 ppm, or a serum thiocyanate greater than 70 micromol per litre were considered as evidence of current cigarette consumption and classified patients as current smokers irrespective of their claimed smoking habit.



### **3.4.6. Hypothalamic-Pituitary-Adrenal Function.**

Hypothalamic-Pituitary-Adrenal function (HPA) was assessed by the measurement of 24 hour urinary free cortisol and by the adrenal response to an injection of tetracosactrin.

#### *24 hour urinary cortisol measurement.*

Patients were asked to collect urine over the 24 hours prior to their laboratory visit. This was done on one occasion during the baseline and after each of the active treatment phases. The patients were instructed to empty their bladders on rising on the morning of the day of collection. This urine was discarded and all subsequent urine passed for the next 24 hours was collected in the container provided. At the end of the 24 hour period the patients were asked to empty their bladder and to save the urine in the bottle, and then to collect no further samples.

#### *Tetracosactrin test.*

10ml of venous blood was withdrawn in to a heparinized tube via a 21 or 19 gauge butterfly needle. The patient then received a slow intravenous injection of 0.25 mg Tetracosactrin over 10 to 15 minutes. 30 minutes after the end of the injection a further 10 ml sample of venous blood was withdrawn. Serum cortisol levels were measured on these samples.

In patients who objected to an injection, a single baseline venous blood sample was withdrawn for the estimation of random unstimulated serum cortisol.

Cortisol in urine and serum was measured in the Department of Clinical Chemistry, East Birmingham Hospital, by a in house radioimmunoassay. Unfortunately this test showed interference with metabolites of oral prednisolone in the urinary samples collected at the end of the third treatment phase.



### **3.4.7. Skin prick tests.**

As part of the baseline investigations all patients had a series of standard skin prick tests performed to *D.Pteronyssinis*, *Aspergillus fumigatus*, cat fur, dog hair, grass pollens, *Cladosporium sp.* and *Penicillium*, to a negative (diluent) and a positive (histamine) control. A positive test was considered to be a wheal of greater than 3 mm diameter over that seen to the negative control.

### **3.4.8. Assessment of Oral Candidiasis.**

On the final pre treatment visit during the baseline period and on each post treatment visit an assessment of oropharyngeal candidiasis was made by simple visual inspection of the oropharynx. A five point scale was used to score the appearances. This was as follows;

- 0 = normal mucosa,
- 1 = small isolated patches of reddened mucosa (less than 0.5 cm diameter),
- 2 = larger confluent reddened areas,
- 3 = areas of white exudate,
- 4 = frank alteration,

Swabs were taken if clinically indicated.

### **3.4.9. Assessment of dysphonia.**

In addition on the final baseline visit and each subsequent visit patients were asked if they had experienced any persistent hoarseness of the voice. This was scored, if present, on an empirical scale as follows;

- 0 = none,
- 1 = mild,
- 2 = moderate,
- 3 = severe.

### **3.4.10. Modified Respiratory Symptom Questionnaire.**

(see appendix I).

At the start of the study the patients completed a doctor administered questionnaire concerning respiratory symptoms. This included modified questions from the MRC respiratory symptoms questionnaire, in addition to questions taken from a questionnaire of Mortagy et al(165), which purport to detect bronchial hyperresponsiveness in patients.

Patients were defined as suffering from chronic bronchitis if they answered positively to questions three and six.

A breathlessness score was derived from the answers to questions 7 to 9. For each positive answer to the graded questions 7 to 9 a score of one was deducted from a maximum score of three. Hence severely disabled patients scored zero, whereas patients with relatively few symptoms from their disease could score 2 or 3.

The answers to questions 16 and 17 were combined to give an indication of a possible 'asthmatic' element to their disease. Patients answering yes to both questions, 'Have you ever had attacks of shortness of breath with wheezing?' and 'Is/was your breathing absolutely normal between attacks?' were classed as having asthmatic features to their disease, all other patients as having no asthmatic features.

Bronchial irritability was defined as described by Mortagy et al(165). Any patient reporting wheeze or breathlessness or both to any of the factors detailed in question 27 were defined as having bronchial irritability.

### **3.4.11. Quality of Life Questionnaire.**

(see appendix II).

On the final baseline visit and after each of the treatment phases the patients answered a doctor administrated quality of life questionnaire. This was developed in Canada by Guyatt et al(166) in



a group of patients with chronic airflow obstruction. This was kindly supplied by this group with an instruction manual and tape for use in this study. The questionnaire consisted of five questions designed to measure the dyspnoea experienced by the patient during every day activities. A further fifteen questions covered three further broad areas of the patients life. These were mastery over the disease, emotional function and fatigue. Questions were read by the investigator word for word from the questionnaire, and the patient answered by indicating from cards the response which best described him/her. Responses were structured on a seven point Likert scale.

The activities causing dyspnea in each patient were volunteered or selected by the patient from a list of activities of daily living. This section of the questionnaire was thus individualised. Patients with milder disease were in some cases unable to select five activities consistently causing breathlessness. In individuals who selected less than five activities the score for this dimension was adjusted for the purposes of presenting the results, by dividing the total score by the number of dyspnea questions answered and multiplying the result by five.

It would be incorrect to compare the results of the dyspnea dimension between patients because the questions are not standardised, as a consequence of the individualisation of the activities. Thus the dyspnea induced by making a cup of tea in a patient with severe disease may be the same as that caused by walking 100 yards briskly in a patient with mild disease. The nature of the dyspnea dimension of the questionnaire is such that the magnitude of the task attempted is not taken into account, and hence only within patient comparisons are possible.

#### **3.4.12. Oxygen Cost Diagram.** (see appendix III).

On two occasions during the baseline period and at the end of each treatment phase patients were asked to complete a modified oxygen cost diagram(167). This consists of a visual analogue scale

with descriptive phrases at various points along the line corresponding to the oxygen requirements of the activities. The top of the line represented 'no breathlessness', the bottom 'the greatest breathlessness'. The patient was instructed to 'mark the line at a point above which you would become breathless'. The original oxygen cost diagram measured 100mm in length, that used in this study was elongated to 198mm to improve clarity, but the relative position of the phrases along the elongated line was maintained. The distance from the bottom of the scale to the patients mark provided an measure of the patients dyspnea.

#### **3.4.13. Diary Card Data.** (see appendix IV).

Throughout the study, from day 1 of the baseline period to the end of the follow-up period, patients were asked to record various items on a diary card on a daily basis. These were

##### *a) Peak expiratory flow rate (PEF).*

Patients were provided with a new Mini Wright peak flow meter and instructed in its use. They were asked to record the PEF on 4 hourly, starting immediately on rising. They were instructed to make 3 readings, and only if the two top readings were within 20 l/min of each other, to record the highest 3 readings. If this criteria was not met they were asked to take further readings until this criteria could be fulfilled. The result was recorded in the appropriate space in the diary card.

##### *b) Breathlessness Score.*

At the end of the day patients were asked to record their breathlessness on a 7 point open ended scale. The lowest value of the scale 1, was chosen to represent a state of not at all breathless, where as the maximum score 7, was described as the worse breathlessness the patient had ever experienced. Patients were instructed to record the number which best described them over the previous 24 hours at the end of the day.

*c) Sputum Assessment.*

Sputum production was assessed simply on a 4 point scale as follows:

- 0 = none
- 1 = on rising only
- 2 = less than one egg cup full all day
- 3 = greater than one egg cup full all day.

Sputum colour was assessed on a 5 point scale:

- 0 = none
- 1 = clear/white/grey
- 2 = yellow
- 3 = yellowish green
- 4 = green.

Patients were instructed to record both sputum production and sputum colour at the end of the day.

*d) Medicine for Bronchitis.*

The investigator recorded on the diary card all medication taken for the patients chest complaint. Patients were instructed to record at the end of the day the amount (number of tablets or puffs) of each medication taken in the previous 24 hours.

### **3.5. DATA HANDLING AND ANALYSIS.**

Data was recorded directly at the time of the visit in individual patient booklets. At the end of the study the data collected was extracted manually onto a spreadsheet and subsequently entered on to a data base on an Elonex 386 laptop personal computer. Data entry was performed in duplicate. The duplicate data entry was cross checked for data entry mistakes, and data ranges for each variable

examined for possible errors in extracting data from booklet to spread sheet.

The subjective data recorded on diary cards was averaged over the final seven days of each phase, and the mean used for subsequent analysis. Peak flow readings were analysed daily, calculating the mean, maximum, and minimum for each day. The diurnal variation was calculated daily as the difference between the daily maximum and minimum divided by the daily mean, expressed as a percentage.

ie, daily diurnal variation in PEF

$$= \frac{\text{daily max PEF} - \text{daily minimum PEF}}{\text{daily mean PEF}} \times 100\%$$

The calculated daily values were averaged over the final seven days of each treatment period to give the diurnal variation (% mean), used in subsequent analysis. The mean diurnal variation calculated in this way was also expressed as a percentage of the predicted PEF for each individual patient,

diurnal variation in PEF (% predicted) =

$$\frac{\text{diurnal varn in PEF}(\% \text{ mean}) \times \text{mean weekly PEF(l/min)}}{\text{predicted PEF (l/min)}}$$

Preliminary data from the diary cards concerning use of medication and sputum production and colour showed little effect of treatment, and had a large percentage of incomplete data, hence no further analysis was performed on this data.

### **3.5.1. Statistical Analysis.**

The aims of the study described above were analysed using end points defined during the design of the study to enable the primary and subsidiary aims to be assessed. The actual analysis employed is described in each chapter.

Analysis was carried out using the Solo(168) and SPSS-



PC(169) statistical programs on an Elonex 386 laptop personal computer. A probability level of 0.05 was considered statistically significant.

Predicted lung function values were derived from the published equations of the European Community for Coal and Steel(170).

## **4. DEMOGRAPHIC DETAILS, LUNG FUNCTION AND RESULTS OF BASELINE SYMPTOM QUESTIONNAIRE.**

### **4.1. ANALYSIS.**

Data for continuous normally distributed data is presented as the mean (SEM), or geometric mean for serum IgE level, and PD20 which showed a log normal distribution. Ranges for continuous data are also presented. Possible relationships between baseline variables were investigated by deriving Pearson or Spearman correlation coefficients as appropriate. Differences between groups of patients (eg; smokers and ex-smokers) in continuous variables were investigated by unpaired Student *t* tests, or Mann Whitney U test as appropriate, and for categorical data by a Chi squared test.

Patient groups were defined on the basis of answers to questions in the baseline symptom questionnaire that suggested asthmatic features to the disease. Affirmative answers to questions 16 'Have you ever had attacks of shortness of breath with wheezing ?' and question 17 'Is/was your breathing normal between attacks ?' when combined were considered suggestive of significant asthmatic features, and patients responding positively to both questions were classed as having asthmatic features present. In addition patients were classified into the presence or absence of bronchial irritability as defined by Mortagy et al(165).

## 4.2. RESULTS.

One hundred and twelve patients entered the baseline period of the study. Seven did not continue into the placebo period because of inability to complete the diary card or follow the protocol (3 patients), or due to an infective exacerbation of their disease during the baseline period requiring treatment with antibiotics and oral corticosteroids (4 patients).

### 4.2.1. Demographic data.

The demographic, smoking and atopic characteristics of the 105 patients who were recruited to the study are shown in table 4.1..

The majority of the study group were male, and nearly one half were current smokers. The average cigarette consumption of those smokers and ex-smokers was moderately high at nearly 50 pack years (1 pack year equals smoking twenty cigarettes per day for one year).

Table 4.1. Demographic data, smoking details and atopic characteristics of the 105 patients at baseline.

	Mean (SEM) or number	Range
Male (female)	75 (30)	
Age (years)	66 (0.6)	49 - 78
Height (m)	1.66 (0.08)	1.46 - 1.85
Weight (kg)	64 (1.3)	39 - 97
Smoking status [as number (%)]		
Current	47 (45)	
Ex smokers	57 (54)	
Never	1 (1)	
Cigarette consumption (pack years)	49 (3.06)	0 - 180
Number skin test positive (%)	23 (22)	
Serum IgE (ku/l) as geometric mean	75	25 - 4810

The results of the skin testing and serum IgE estimations indicate heterogeneity with respect to these allergic characteristics. Twenty three of the patients had positive skin tests to common airborne allergens. No relation between age, or smoking habit and skin test reactivity was seen (mean [95% CI] age (years); skin test positive 66 [64.5-67.5], skin test negative 65 [62-67.5]: % group skin test positive; current smokers 23%, ex smokers 21%). The geometric mean serum IgE level was raised above the laboratory normal upper limit at 75 ku/l. Thirty six patients had a serum IgE level over 100 ku/l. IgE levels in smokers and ex smokers were similar (geometric mean [range] serum IgE ku/l; current smokers 80 [25-4810], ex smokers 72 [25-860]).

#### **4.2.2. Baseline pulmonary function.**

The details of the baseline prebronchodilator pulmonary function tests are given in tables 4.2 and 4.3, and the distribution of the mean baseline prebronchodilator FEV1, and volume corrected carbon monoxide gas transfer (KCO) in figures 4.1. and 4.2.. The latter are shown as the percentage of the predicted value.

The results of the baseline spirometry show a wide range of airflow obstruction (table 4.2.). A few patients had extremely severe obstruction with FEV1 values of less than 500ml, and FEV1/FVC ratios of less than 25%. The average FEV1 and FEV1/FVC ratio indicate that the group studied had moderately severe disease. There was no significant difference in the absolute level of FEV1 between smokers and ex smokers (mean [95% CI] FEV1 (litres); current smokers 1.08 [0.95-1.22], ex smokers 1.03 [0.9-1.14]), neither was a correlation between the amount smoked, as estimated from the questionnaire in pack years, and FEV1 or FEV1/FVC ratio observed (FEV1  $r=0.05$ ; FEV1/FVC  $r=-0.09$ ). Ex smokers did show a slightly lower FEV1/FVC ratio however (mean(SEM) FEV1/FVC ratio, smokers 41.7%, ex smokers 37.0%; 95% confidence limits for difference -3.7 to 9.5%).

Static lung volumes in general showed hyperinflation and a raised residual volume reflecting the severity of the airflow

obstruction.

Table 4.2. Prebronchodilator spirometry and static lung volumes in the 105 patients (as mean (SEM) and range unless indicated).

	Mean (SEM)	Range
FEV1 litres	1.05 (0.05)	0.3-2.21
% predicted	40 (1.5)	15-66
FVC litres	2.67 (0.08)	1.35-4.89
as % predicted	81 (1.4)	53-120
FEV1/FVC ratio	39.2 (1.2)	15.8-65
TLC litres	6.4 (0.13)	2.82-10.60
as % predicted	109 (1.7)	59-161
FRC litres	4.65 (0.11)	1.84-8.14
as % predicted	144 (2.9)	69-225
RV litres	3.64 (0.09)	1.44-6.0
as % predicted	161 (4.2)	65-287

Single breath carbon monoxide gas transfer measurements were impaired in the majority of the patients studied (table 4.3.). This was true both for the diffusion coefficient for the whole lung, TLCO, and the volume corrected value, KCO. Again however a wide range of values were recorded reflecting the spectrum of disease seen in the clinic setting (figure 4.2.).

No correlation was seen in the baseline data between smoking category and KCO (mean [95% CI] KCO (mmol/kPa/min/l); current smokers 1.03 [0.91-1.15], ex smokers 1.02 [0.92-1.12]), or between the past cigarette consumption and this measure of gas transfer ( $r=-0.12$ ).

Table 4.3. The results of single breath carbon monoxide gas transfer measurements ( as mean (SEM) and range unless indicated).

	Mean (SEM)	Range
TLCO mmol/kPa/min as % predicted	5.46 (0.23) 68 (2.6)	1.1-10.8 15-125
KCO mmol/kPa/min/l as % predicted	1.03 (0.04) 58 (2.3)	0.24-1.81 14-113

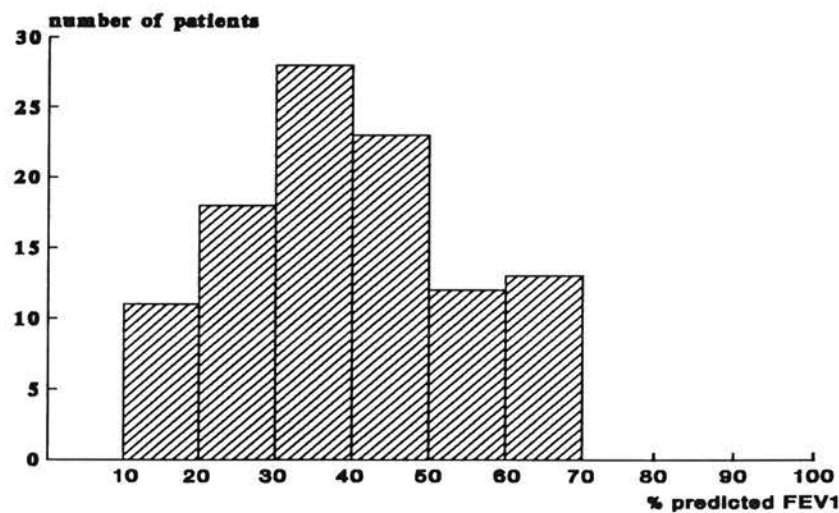


Figure 4.1. The distribution of prebronchodilator FEV1 (as % predicted) in the patients studied.



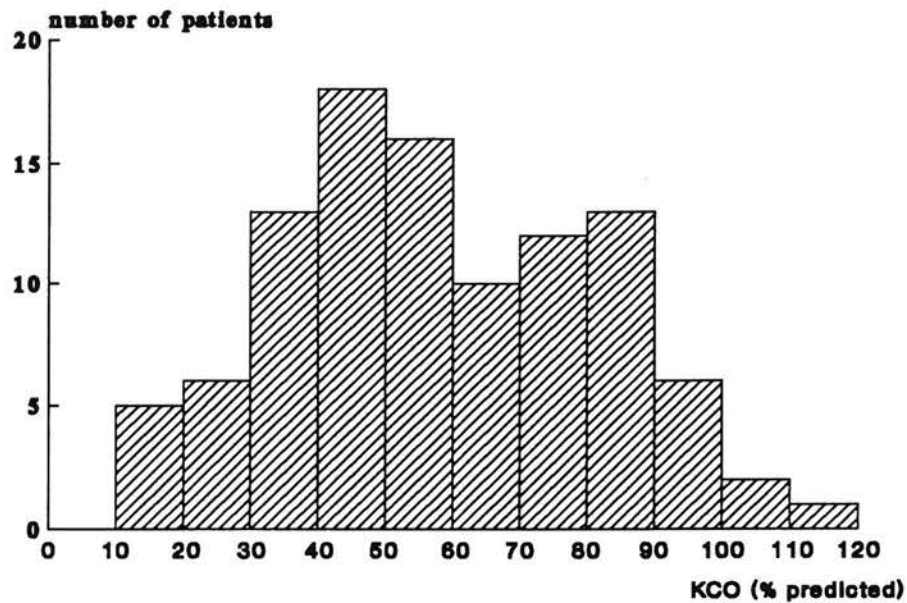


Figure 4.2. The distribution of the volume corrected carbon monoxide gas transfer (KCO), as a percentage of the predicted value.

#### 4.2.3. Variability and reversibility of airflow obstruction, and bronchial hyperresponsiveness to inhaled histamine.

Measurements of variability in lung function, both spontaneous and drug induced are given in table 4.4.. These might be considered a measure of the asthmatic component of the airflow obstruction in the group.

The diurnal variation in PEF was over 15% in the majority of patients when expressed as a percentage of the mean PEF. However as a percentage of the predicted PEF the average diurnal variation in PEF was only 11%.

Table 4.4. Peak expiratory flow, reversibility and variability of lung function, and bronchial responsiveness to inhaled histamine in those patients with data (as mean (SEM) and range in 105 patients unless indicated).

	Mean (SEM)	Range
Peak expiratory flow rates (n = 104)		
mean PEF l/min	233 (8.7)	78-473
as % predicted	54 (1.7)	22-99
Diurnal variation in PEF		
as % mean	21 (1.0)	4.6-60
as % predicted PEF	11 (0.6)	1.7-36
Reversibility in FEV1 to 200mcg salbutamol		
absolute change (ml)	144 (13)	-160 to 620
% baseline	18.3 (1.8)	-13.9 to 85
% predicted FEV1	5.7 (0.5)	-6.8 to 22.3
% 'possible'	9.6 (1.2)	-19 to 72.5
to 80mcg Ipratropium bromide		
absolute change (ml)	127 (15)	-260 to 710
% baseline	14.4 (1.6)	-29 to 59.7
% predicted	4.8 (0.6)	-9.2 to 26
Bronchial responsiveness to inhaled histamine (n = 74)		
PD20 umol	0.52	0.04-16
as geometric mean		

The reversibility in FEV1 to both bronchodilators also depends on the method used to express this, but the average absolute change was small (less than 150ml). Frequency histograms of the change in FEV1 following 200mcg salbutamol, as the four expressions of reversibility calculated are shown in figure 4.3. and 4.4.. Only two patients showed an improvement in FEV1 of over 450ml after salbutamol (figure 4.3.). Although when expressed as a percentage of the prebronchodilator FEV1 a number of patients

appear to have reversible airflow obstruction, when the effect of a low prebronchodilator FEV1 is removed by expressing the change as a percentage of the predicted FEV1, the group show little reversibility (figure 4.4.). The expression of reversibility as a percentage of the capacity to respond, % 'possible' (change in FEV1 / predicted - prebronchodilator FEV1), showed only one patient who improved his FEV1 by over 50% of this measure after salbutamol.

The mean (SEM) FEV1 after 200 mcg salbutamol was 45.4 (1.5) percent of the predicted value, indicating that the majority of patients had a significant degree of irreversibility to their airflow obstruction. A frequency histogram of post salbutamol FEV1 values is shown in figure 4.5..

Bronchial responsiveness to inhaled histamine (PD20) was measured in 74 patients who had an FEV1 greater than 0.75 litres. In 3 patients the FEV1 fell by less than 20% after the highest dose given, and the value for these patients was derived by further extrapolation as explained in the methods. In one patient the value was truly censored, in that a value could not be obtained by extrapolation, therefore a value of 16 micromol, the maximum possible, was assigned to this patient. As a group bronchial hyperresponsiveness was moderate. Further details of bronchial hyperresponsiveness to inhaled histamine in this group of patients is given in chapter 8.

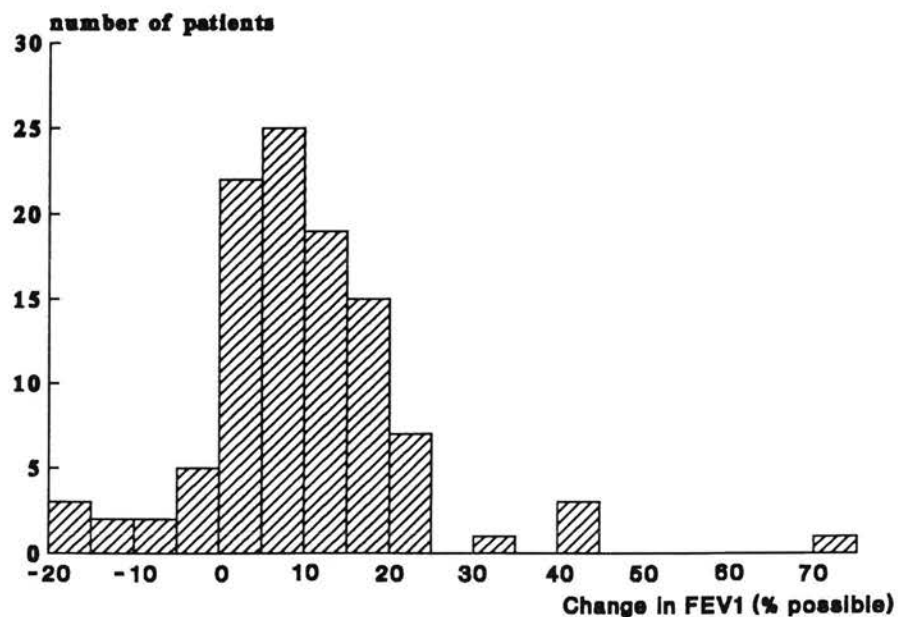
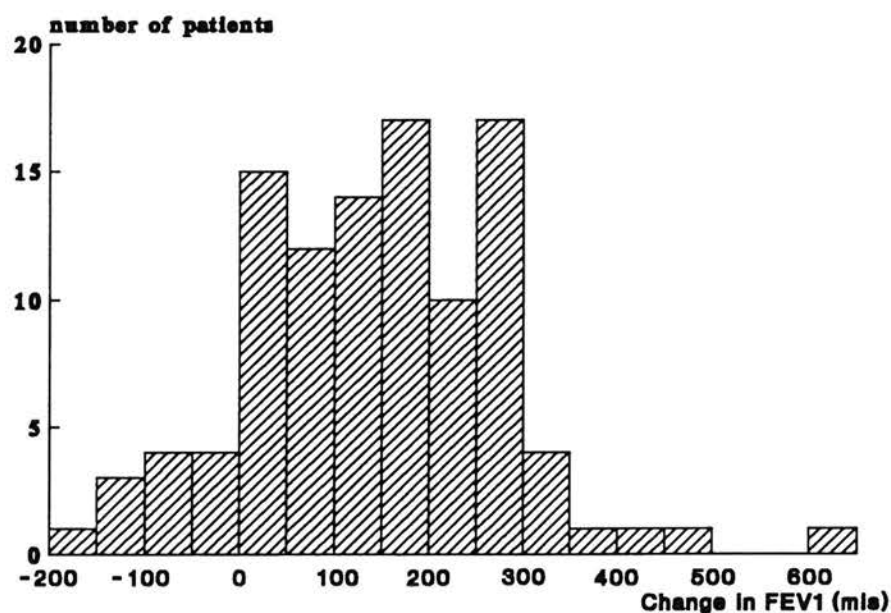


Figure 4.3. The distribution of reversibility of FEV1 after 200mcg salbutamol, shown as the absolute change ( upper graph), and as a percentage of the 'possible' reversibility (lower graph).

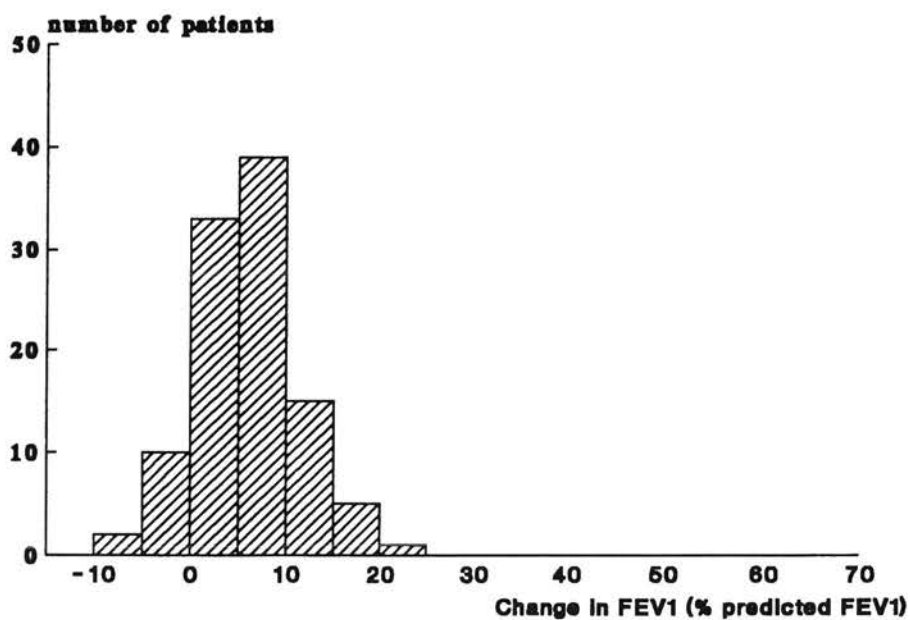
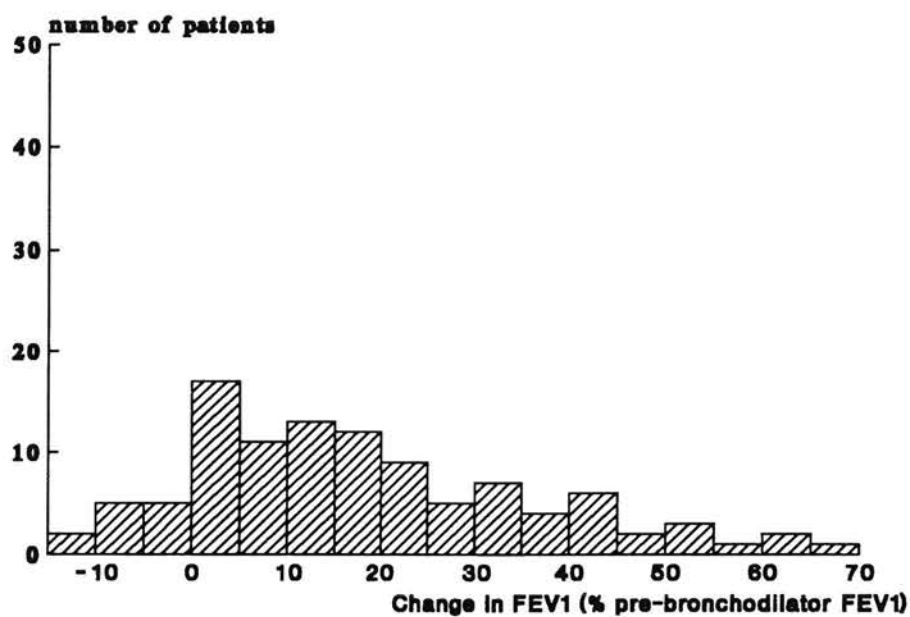


Figure 4.4. The distribution of reversibility of FEV1 after 200mcg salbutamol, as a percentage of the pre-salbutamol FEV1 (upper graph), and as a percentage of the predicted FEV1 (lower).

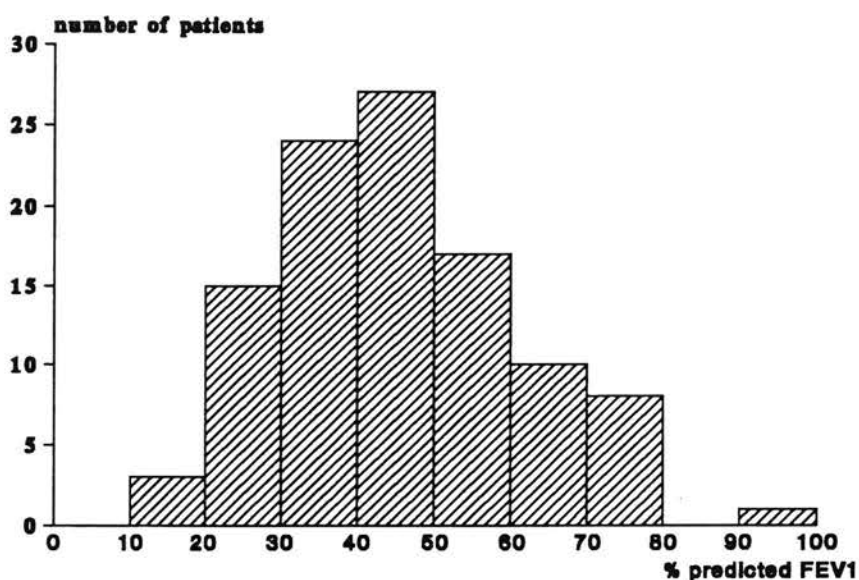


Figure 4.5. The distribution of post salbutamol FEV1 (as % predicted) in the 105 patients studied.

#### 4.2.4. Baseline respiratory symptom questionnaire data.

Responses to selected questions of the baseline questionnaire are tabulated in table 4.5.. The majority of the patients studied had a chronic productive cough for at least three months of the year. Just over a third of patients experienced breathlessness walking at their own pace on level ground. Only 7 patients, with less impaired lung function, felt free of significant symptoms.



Table 4.5. Responses to selected questions of the baseline respiratory questionnaire (as number[%]).

Chronic productive cough on most days for at least three months of the year)	69 (66%)
Breathlessness score (question 7-9)	
0	40 (38%)
1	25 (24%)
2	33 (31%)
3	7 (7%)
'Have you ever had attacks of shortness of breath with wheezing ? (Question 16)	
Yes	53 (51%)
No	52 (49%)
Was your breathing absolutely normal between attacks ? (Question 17)	
Yes	38
No	15
'Bronchial irritability'	
Present	43 (41%)
Absent	62 (59%)
Positive answers to 'Have you ever had	
bronchitis	71 (68%)
bronchial asthma	16 (16%)
hay fever	9 (9%)
eczema	12 (11%)

For breathlessness score lower scores indicate breathlessness on lighter exertion.

#### **4.2.5. Comparison of lung function in the defined subgroups.**

The answers to questions 16 'Have you ever had attacks of shortness of breath with wheezing ?' and question 17 'Is/was your breathing normal between attacks ?' when combined could be treated as an indicator of an underlying 'asthmatic' element to the disease. Just over half the patients experienced wheezy attacks, but only 38 of the 53 patients reporting such attacks felt that their breathing was normal between attacks. These 38 patients showed no significant differences in any objective measure of baseline lung function including reversibility and variability or carbon monoxide gas transfer compared to the remaining patients (table 4.6.). Of the 38 patients 29 reported a chronic productive cough in addition to the complaints of wheezing. Serum IgE levels were also similar in patients with and without asthmatic features (geometric mean serum IgE (ku/l) asthmatic features present 92; absent 67).

Bronchial irritability as defined by Mortagy et al(165) was present in 43 patients, in 29 of these patients the answers to question 16 and 17 were also positive, that is they reported asthmatic features to their disease. Twenty five of the 43 patients reported a chronic productive cough in addition to symptoms of bronchial irritability. The patients with bronchial irritability showed lower mean FEV1 values, more airflow obstruction, and a decreased mean PEF compared to the patients without this syndrome. Measurements of reversibility and PEF variability were similar in both groups (table 4.7.).

Table 4.6. Lung function in patients with and without asthmatic features. Patients answering questions 16 and 17 (see text) positively classed as asthmatic features present. (As mean (SEM) unless indicated).

Asthmatic features	Present (n=38)	Absent (n=67)
FEV1 litres	1.12 (0.08)	1.01 (0.06)
FEV1/FVC %	40.4 (2.0)	38.6 (1.5)
mean PEF l/min	247 (13.5)	226 (11.3)
PD20 umol (geometric mean)	0.46 (n=31)	0.57 (n=43)
Reversibility of FEV1 to 200mcg salbutamol absolute change (ml) as % predicted FEV1	155 (23) 5.9 (0.9)	138 (16) 5.6 (0.7)
Diurnal variation in PEF as % mean as % predicted	21 (1.9) 11 (1.1)	21 (1.2) 10.6 (0.7)
TLCO (mmol/kPa/min) as % predicted	5.2 (0.3) 66.2 (3.4)	5.8 (0.4) 71.2 (4.2)
KCO (mmol/kPa/min/l) as % predicted	1.01 (0.05) 56.5 (2.9)	1.06 (0.06) 61.1 (3.5)

No significant differences.

Table 4.7. Lung function in patients with and without 'bronchial irritability' as defined. (As mean (SEM) unless indicated).

	Bronchial Irritability	
	Present (n=43)	Absent (n=62)
FEV1 litres	0.91 (0.06)	1.15 (0.06) *
FEV1/FVC %	34.5 (1.8)	42.5 (1.5) *
mean PEF l/min	212 (13.3)	249 (11.23) *
PD20 umol (geometric mean)	0.56 (n=25)	0.49 (n=49)
Reversibility of FEV1 to 200mcg salbutamol absolute (ml)	138 (17)	149 (19)
% predicted	5.6 (0.7)	5.8 (0.8)
Diurnal variation in PEF % mean	21 (1.5)	20 (1.4)
% predicted	10 (0.8)	11.2 (0.8)

\*  $p < 0.05$ , all other comparisons non significant.

### 4.3 DISCUSSION.

The patients were recruited from a heterogeneous clinic population in an attempt to reflect the clinical problem facing physicians. The major cause of their airflow obstruction was cigarette smoking, but a few patients had other current or past medical problems which may have contributed to the airflow obstruction seen. Three patients in addition to past or current heavy cigarette consumption also had post tuberculous scarring of the lungs, two had coexistent rheumatoid arthritis - another possible cause of airflow obstruction - and two patients produced copious amounts of sputum, suggesting bronchiectasis as an additional underlying pathology.

It could be argued that the 'lumping' of different pathologies together is counterproductive. The effects of treatment may not be the same in different disease states, and by including in the study population patients who may not have 'pure' smoking related airflow obstruction the effects of treatment on this group may be less obvious. However distinguishing between the different causes, or the contribution of different pathological processes in an individual patient with chronic airflow obstruction is difficult(171). The overriding concern must be to ensure that the patient receives the most effective treatment. The aim of this study therefore was to examine the effects of treatment in a group of patients with chronic airflow obstruction in whom the primary diagnosis was not asthma, but who would normally undergo a 'trial of steroids'(41). By excluding patients with asthma in whom the benefit of such treatment is not in doubt, the patients studied formed a well defined group familiar to clinicians.

Definitions of asthma vary widely, from vague statements about symptoms to more specific physiological criteria. The American Thoracic Society (A.T.S.) definition is lengthy, and is not easily translated into clinical practice,

'...a clinical syndrome characterised by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are

paroxysms of cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). The primary physiological manifestation of this hyperresponsiveness is variable airways obstruction. ....' (37).

Later statements in the same document suggest the age at onset of symptoms, family and personal history of allergic disease, and identified specific precipitators to bronchoconstriction may help suggest the diagnosis in a patient with wheeze, chest tightness and a reduced FEV1/FVC ratio.

In a study of the factors that determine diagnostic labelling of patients with chronic airflow obstruction a large degree of reversibility in FEV1, and a return of the airways obstruction to normal or near normal values either spontaneously or after a bronchodilator appeared to be the major diagnostic criterion used (172). The authors of this study later proposed a classification system for patients with chronic airflow obstruction in which asthma was favoured if symptoms resolved rapidly, if the variability in PEF was greater than 15% of the mean PEF, if markers of atopy were present in the patient, and if the patient exhibited marked bronchial hyperresponsiveness to inhaled agents (172). These criteria are similar to those proposed by the A.T.S., quoted above.

It may therefore be instructive to examine the population under study for these characteristics, to determine if, inadvertently, undiagnosed asthmatics have been included in the study group. A later chapter will examine the influence of such features on response to inhaled beclomethasone.

The patients studied for this thesis were elderly reflecting the insidious onset and progression of the process producing chronic airflow obstruction. In all patients studied the symptoms had begun late in adult life, and had been present for over five years. All but one had been or were cigarette smokers (the single never smoker complained of persistent breathlessness, and cough and sputum production, but denied wheeze or acute attacks of breathlessness). The proportion of smokers and ex smokers, and their cigarette consumption were similar to that seen in longitudinal studies of



chronic airflow obstruction in the population(36).

The prevalence of positive skin tests, and the apparently high mean serum IgE level in the patients may indicate that a high proportion of atopic individuals have been recruited to the study, and be construed as evidence for the inclusion of a significant number of asthmatics into the study population. However the prevalence of positive skin tests in this group is again similar to that seen in Burrows subjects with 'pure' chronic obstructive pulmonary disease (COPD) in the Tucson longitudinal study(173). It is much less than the prevalence of skin test positivity in subjects with asthma from the same study(174), and appears to be similar to the prevalence of skin test positivity in the general population of Tucson aged 50 years and over(175). Hence on these considerations the number of patients with positive skin tests is not unexpected, and does not suggest the inclusion in my study population of undiagnosed asthmatics.

Serum IgE levels fall with age(175), and are increased by smoking(176). Burrows et al have shown that in older skin test negative smokers with chronic cough and sputum production higher IgE levels correlate with reduced FEV1 levels(177). However they have also demonstrated a correlation between age-sex standardised serum IgE and a diagnosis of asthma. Hence it is clear that the relationship between serum IgE and respiratory dysfunction is complex, and not simply because of asthma. Because of differences in the technique used to measure serum IgE it is difficult to compare levels in this study with values reported in the literature. It may be that chronic airflow obstruction associated with smoking operates via an IgE dependent mechanism, or that the increase in serum IgE seen in smokers is a paraphenomenon. However the serum IgE level in a patient with chronic airflow obstruction is a poor indicator of an asthmatic component to the disease.

Reversibility of FEV1 to bronchodilators and diurnal variation in PEF are often suggested as markers of asthma(37). Both reversibility and PEF variability are usually expressed as a percentage of the prebronchodilator or mean value respectively.

However by expressing a change in the variable as a percentage of the starting level, small changes in the variable take on undue significance in patients with low starting values. This applies both to reversibility of FEV1 to bronchodilators and PEF variability. Hence a 200ml improvement in FEV1 after salbutamol is a 20% increase in a patient with a starting FEV1 of 1000ml, but only 5% in a patient with an FEV1 of 4000ml. In patients with more impaired lung function the normal values for FEV1 reversibility derived from relatively normal populations may not be applicable. Expressing change in these patients as a percentage of the predicted value is independent of the initial value, and probably preferable(159,178).

The measured reversibility to a beta 2 agonist and an anticholinergic agent in this group of patients showed mean absolute changes which were less than the short term variability in measurement of FEV1 and FVC previously published(94,179), although some individual patients did show greater changes (figure 4.3.). Only one patient had airflow obstruction which could have been considered reversible (figure 4.5.), in that the post salbutamol FEV1 was greater than 80% of the predicted FEV1. However this individual had a FEV1/FVC ratio of less than 50%, unchanged by bronchodilation, and a volume corrected carbon monoxide gas transfer (KCO) of less than 50% predicted, suggesting significant non asthmatic disease. As a group the mean post salbutamol FEV1 was less than half the predicted value.

Expressing the reversibility of FEV1 as a percentage of the 'possible' reversibility may also give an indicator of the asthmatic nature of the disease. Patients with high values of this index could be considered asthmatic, in that their airflow obstruction is close to fully reversible, a feature which many physicians feel suggests asthma as the underlying diagnosis(171). The mean value for this expression of FEV1 reversibility was less than 10%, and 75% of the patients studied had values for this index of less than 15%. These results do not suggest the inclusion of a significant number of undiagnosed asthmatics in the study population.

In a study of patients with asthma and non asthmatic chronic

airflow obstruction Meslier et al suggested that an increase in FEV1 of over 15% of the predicted FEV1, or 450ml in absolute terms was relatively specific for identifying patients with asthma(180). Although such strictly defined limits are probably too rigid, only 6 patients showed an improvement in FEV1 of greater than 15% of the predicted FEV1 after salbutamol and only 2 patients showed an increase in FEV1 of over 450ml after salbutamol. Hence the reversibility characteristics of the group as a whole do not suggest a significant proportion of the patients studied have undiagnosed asthma.

The reversibility of FEV1 to bronchodilators in the patients studied was similar to that reported from larger studies of patients with chronic airflow obstruction published in the literature(181,182). In the large IPPB trial in the US the mean change in FEV1 following bronchodilator was 15% as a percentage of the initial prebronchodilator value, or 5.1% as a percentage of the predicted FEV1(180). A wide range of reversibility was seen in the IPPB study with the standard deviation of the distribution approximating the mean, similar to the results reported here.

Hetzel and Clark suggested a diurnal variation in PEF of over 20% of the mean value was suggestive of asthma(183). However Lebowitz et al have recently found in a larger study, that the upper limit of normal for variability in PEF was 19% of the mean PEF(184). Hence Hetzel and Clark's earlier conclusions may not be correct, and in terms of diurnal variation in PEF, the daily variability in PEF seen in my study, when expressed as a percentage of the mean daily value, is probably just outside the normal range. It is similar to that reported by Dawkins and Muers in a smaller number of patients with chronic airflow obstruction, 24% of the mean daily value(185). It is also similar to the diurnal variation in PEF seen in a large Dutch study of patients with asthma and chronic airflow obstruction recently reported(186). This study found similar values for diurnal variation in PEF in patients with asthma and chronic airflow obstruction, with a mean diurnal variation in PEF in all the patients of 15% of the mean daily value. Their results would suggest that PEF variability is not a good discriminator between asthma and non

asthmatic chronic airflow obstruction.

On the basis of objective tests of lung function therefore the majority of patients appeared to have a non asthmatic form of chronic airflow obstruction. In terms of symptoms it could be argued that positive answers to questions 16 and 17 may indicate possible underlying asthma. A history of wheezing is not specific for asthma, but this in addition to 'normal' breathing between attacks may signify asthma. Only 38 patients gave positive answers to both questions, and 29 of these also complained of a chronic productive cough, suggesting coexistent chronic bronchitis. However the baseline lung function of the two groups so defined (table 4.6.) shows no differences. In particular both groups show impairment of carbon monoxide gas transfer, suggesting a similar degree of emphysema in both. In addition reversibility of FEV1 to salbutamol, and variability in PEF were similar between the two groups.

Mortagy et al defined a syndrome of bronchial irritability which they implied may predispose to asthma(165). They also suggested patients exhibiting this syndrome with chronic airflow obstruction may show a response to corticosteroids, inferring these are the patients with 'missed asthma' as the cause of the chronic airflow obstruction. The baseline lung function of patients showing the features of this syndrome in my study suggest that in patients with severe chronic airflow obstruction, the main factor relating to the presence of this syndrome is the level of impairment of lung function. Those patients with bronchial irritability had more severe impairment of FEV1 and FEV1/FVC. The two groups showed a similar impairment of carbon monoxide gas transfer however, and FEV1 reversibility to salbutamol, and PEF variability was equivalent between these groups. Like non specific bronchial hyperresponsiveness to inhaled agents, bronchial irritability in patients with severe chronic airflow obstruction appears to reflect the severity of the airflow obstruction rather than hinting at the underlying pathological mechanism.

These comparisons of patient groups defined on symptoms also indicate the difficulty in defining asthma in smokers and ex

smokers with severe chronic airflow obstruction. In this group of patients variability of symptoms, either spontaneous or induced, does not correlate with variability in objective measures of lung function. The main determinant of whether a patient reports certain symptoms appears to be related to the psychological and physical factors which govern the perception of breathlessness and wheeze. It would therefore be unjustified to label a patient asthmatic on the basis of subjective criteria alone, and the objective measures of asthma considered suggest that the criteria for inclusion into this study satisfactorily excluded patients with asthma.

It is difficult to define asthma in clinical and physiological terms in elderly patients for the purposes of selecting patients for clinical trials. Although the criteria chosen for this study were clinically based the analysis performed suggests that the majority of the patents studied did not have what is usually considered to be asthma. They had demographic, atopic and physiological characteristics similar to groups of patients with non asthmatic chronic airflow obstruction studied by other workers. Furthermore the analysis presented in chapter 10 shows that the presence of features commonly thought to indicate asthma does not predict response to steroids in an individual patient.

## **5. RANDOMISATION, WITHDRAWALS AND COMPLIANCE WITH TREATMENT.**

### **5.1 RANDOMISATION AND WITHDRAWALS.**

Fifty three patients were randomised at the end of the placebo period to receive 1500mcg per day of inhaled beclomethasone, and the remainder to receive the higher dose of 3000mcg per day. In total seven patients were withdrawn during the placebo phase, six from the lower dose group, only one from the higher dose group. The reasons for withdrawal are given in appendix V.

All patients entering the first active treatment phase (inhaled beclomethasone alone) completed that phase successfully, and produced evaluable data. Hence 47 patients completed treatment with 1500mcg per day beclomethasone for the three week period, and 51 with 3000mcg per day.

During the second active treatment phase when oral prednisolone 40 mg per day was added to the regime in two thirds of patients, a further six patients were withdrawn (details in appendix V). The number of patients entering and completing each treatment phase is shown in figure 5.1..

The baseline physiological characteristics of the 13 patients withdrawn from the trial were not significantly different from the patients who successfully completed the trial (table 5.1.).



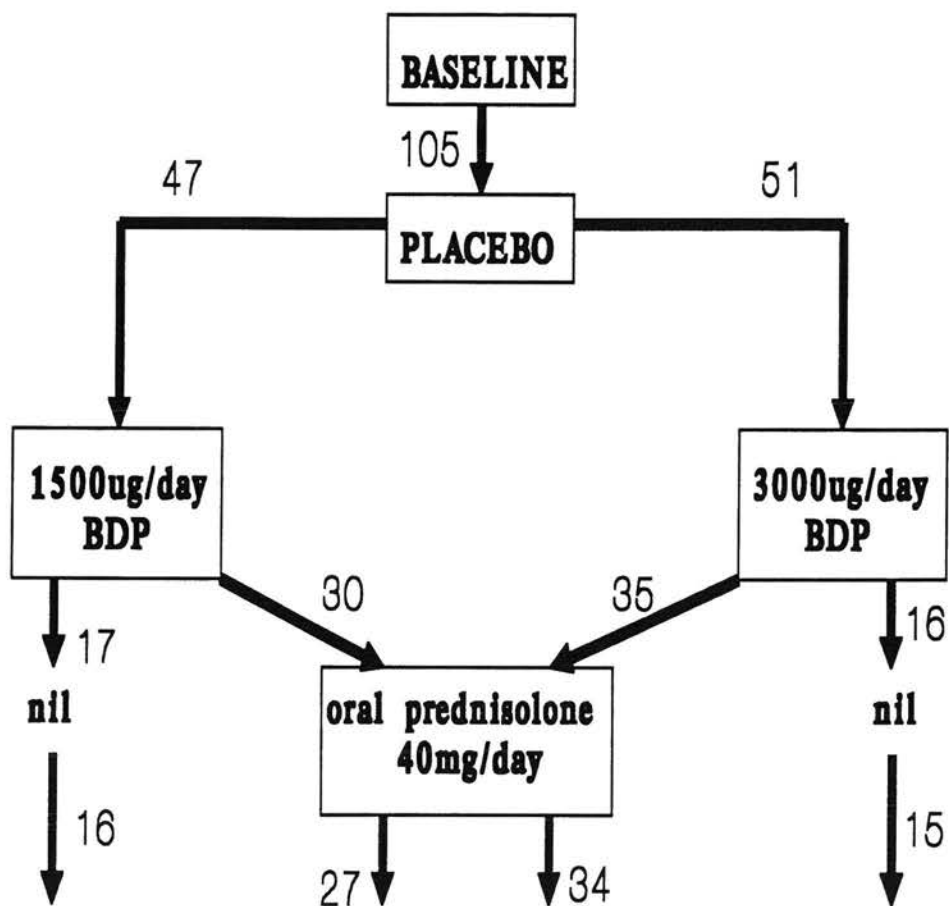


Figure 5.1. Diagrammatic representation of number of patients entering and completing each treatment phase.



Table 5.1. Baseline physiological characteristics in patients withdrawn from the trial, and those completing all three treatment phases. (As mean (SEM) unless indicated).

	Withdrawn (n=13)	Completed (n=92)
Age years	64 (1.6)	66 (0.7)
FEV1 litres	0.99 (0.10)	1.06 (0.05)
FEV1/FVC %	39.1 (3.6)	39.3 (1.3)
mean PEF l/min	212 (13.8)	236 (9.7)
PD20 umol (geometric mean)	0.42 (n=10)	0.54 (n=64)
Reversibility of FEV1 to 200mcg salbutamol absolute (ml)	145 (46)	144 (14)
% predicted	5.5 (1.7)	5.7 (0.6)
Diurnal variation in PEF % mean	19 (2.9)	21 (1.1)
% predicted	9.4 (1.5)	10.9 (0.6)

## 5.2 COMPLIANCE WITH TREATMENT.

Compliance with prescribed trial medication was assessed by weighing inhaler cannisters after return and counting tablets returned.

Full inhaler cannisters weighed approximately 28 grammes, and patients were supplied with two inhalers for each treatment phase. The weight of drug inhaled was calculated by simple subtraction, combining the change in weight for both cannisters. Cannisters were weighed to 0.1 gram.

Two hundred and twenty four tablets were supplied to each patient at the start of each phase of treatment. Returned tablet count gave an estimate of compliance with oral therapy.

For each measure of compliance allowance was made for

differing treatment periods. The trial design allowed a tolerance of +/- seven days for treatment periods, ie treatment periods could last from 14 to 28 days. Therefore the weight of inhaled drug used, and the number of tablets consumed was expressed per day of treatment.

## **RESULTS.**

The median daily change in the weight of the two inhalers was 1 gram, with a 10th centile of 0.77g. For oral therapy the median number of tablets consumed per day was 7.6, with a lower 10th centile of 7.1.

For the purposes of assessing the effect of compliance with treatment on end points, it was decided to classify all patients with a change in weight of both inhalers combined of less than 0.7g as non compliant with inhaled therapy, and all patients taking less than 6 tablets per day as non compliant with oral therapy. On this basis 92 of 98 patients were compliant with inhaled placebo therapy, and 86 of 98 with inhaled therapy during the first active (inhaled beclomethasone) treatment phase. For the final treatment phase 78 of the 92 patients completing this phase were compliant with inhaled therapy, and 86 with oral therapy.

The analysis of effect of treatment was performed on an intention to treat basis. Compliance to treatment appeared good, and preliminary analysis omitting non compliant individuals had little effect on the results and conclusions. Therefore only the intention to treat analysis with all patients included is presented for the remainder of the thesis.

The timing of assessments was within the limits specified in all but two of 282 visits. As this was such a small percentage of the total, this was ignored for the subsequent analysis.

## **6. THE EFFECT OF TREATMENT ON LUNG FUNCTION.**

### **6.1. ANALYSIS.**

A comparison of the baseline characteristics of the dosage groups was performed to detect differences in possible confounding factors affecting response to treatment. Unpaired Student *t* tests were used to compare normally distributed continuous data, Mann Whitney U test for non parametric continuous data, and chi squared test for categorical data.

To compare the efficacy of placebo, inhaled beclomethasone and oral prednisolone on lung function, the FEV1, and FVC, recorded pre bronchodilator on the final day of each treatment phase, and mean PEF recorded over the last 7 days of the treatment phase, were selected as end points. The response to treatment in these physiological variables after inhaled BDP was assessed by a repeated measures analysis of variance, with dose of drug entered as a factor. Where significant effects were detected a Fisher's least significant differences (LSD) test was used to determine which comparisons were significant.

For analysis of the data after the final phase of active treatment, when two thirds of the patients received oral prednisolone in addition to inhaled beclomethasone, the change in each variable from the previous phase was calculated. The change was compared between patients receiving or not receiving prednisolone by an unpaired Student *t* test, combining the inhaled beclomethasone dose groups.

In addition a 'categorical analysis' was undertaken after classifying each patient as a treatment responder or non-responder for each of the three treatment phases.

Response to treatment was defined as an improvement in pre bronchodilator FEV1, or FVC recorded on the final day of each treatment phase, or mean PEF over the last 7 days of the treatment phase of at least 20% when compared to the baseline value. The

difference in response rates to placebo, and inhaled beclomethasone was assessed by a McNemar test. The response rate after the final treatment phase was compared using a Chi squared test for the two final phase treatment groups, again combining the beclomethasone dose groups.

## 6.2. RESULTS.

### 6.2.1. The effect of inhaled beclomethasone.

#### *a. Characteristics of the two inhaled beclomethasone dosage groups.*

No significant differences in the baseline characteristics of the two beclomethasone dosage groups were detected (table 6.1. and 6.2.). In particular the two groups were well matched in terms of degree of airflow obstruction, smoking status and past cigarette consumption, 'asthmatic' variables - diurnal variation in PEF, and reversibility to salbutamol - and atopic characteristics.

Table 6.1. The baseline physiological characteristics of the two beclomethasone treatment groups. As mean (SEM) unless indicated.

	Dose group	
	BDP 750mcg b.d. (n=47)	BDP 1500mcg b.d. (n=51)
Females (number)	15	14
Age (years)	66 (1.0)	65 (1.0)
FEV1 (litres)	1.07 (0.07)	1.05 (0.07)
FEV1 (% predicted)	41.1 (2.2)	39.3 (2.1)
FEV1/FVC %	41.2 (1.8)	37.8 (1.7)
mean PEF (l/min)	231 (12)	236 (13)
TLCO (% predicted)	70.3 (3.8)	67.4 (3.8)
KCO (% predicted)	61.4 (3.4)	56.4 (3.2)
diurnal variation in PEF(% predicted)	10.4 (0.8)	11.0 (0.9)
FEV1 reversibility to 200mcg salbutamol as % predicted FEV1	6.4 (0.6)	5.6 (0.9)

No significant differences.

Table 6.2. The atopic and smoking characteristics of the two beclomethasone treatment groups. As mean (SEM) unless indicated.

	Dose group	
	BDP 750mcg b.d. (n=47)	BDP 1500mcg b.d. (n=51)
Serum IgE (ku/l) (geometric mean)	83	64
Number with positive skin tests (%)	10 (21)	10 (20)
Smoking status [as number (%)]		
Current smokers	17 (36)	28 (55)
Ex smokers	29 (62)	23 (45)
Never smokers	1 (2)	0
Cigarette consumption (pack years)	51 (5.0)	46 (4.1)

No significant differences.

*b. The effect of inhaled beclomethasone on FEV1, FVC and mean PEF.*

A small but statistically significant effect of inhaled beclomethasone on all three physiological measures was seen (table 6.3.). There was no significant difference between the two doses of BDP, and no dose-treatment interaction was detected for any of the three end points used. For both BDP dose groups combined the mean improvement from the baseline value after active treatment was 48ml for FEV1, 120ml for FVC and 12.4 l/min for mean PEF. The average values in each beclomethasone dose group for the three prebronchodilator parameters is shown in table 6.3., with the results of the analysis of variance. For all three variables the results after active treatment with inhaled beclomethasone were significantly higher than those

recorded at baseline or after placebo therapy. In this analysis no statistically significant differences between placebo and baseline were observed.

Table 6.3. Mean (SEM) values for lung function variables at baseline, after placebo and inhaled beclomethasone.

BDP dose	Baseline	Placebo	BDP
<i>FEV1</i> (litres)			
750mcg b.d.	1.07 (0.07)	1.07 (0.07)	1.11 (0.07)
1500mcg b.d.	1.05 (0.07)	1.01 (0.07)	1.10 (0.07)
Treatment Effect F-ratio=11.14, DF=2,192 p<0.0001. Interaction F-ratio=1.35, DF=2,192, ns.			
<i>FVC</i> (litres)			
750mcg b.d.	2.58 (0.11)	2.58 (0.10)	2.68 (0.11)
1500mcg b.d.	2.76 (0.12)	2.78 (0.12)	2.90 (0.11)
Treatment Effect F-ratio=8.63, DF=2,192, p<0.0005. Interaction F-ratio=0.14, DF=2,192, ns.			
<i>Mean PEF</i> (l/min)			
750mcg b.d.	231 (12.6)	235 (13.0)	243 (13.6)
1500mcg b.d.	237 (14.0)	235 (14.4)	250 (14.9)
Treatment Effect F-ratio=16.5, DF=2,188, p<0.0001. Interaction F-ratio=1.14, DF=2,188, ns.			

The mean change in each variable after placebo and BDP is illustrated graphically in figure 6.1. For this graphical presentation both beclomethasone dose groups have been combined. The scatterplots (figures 6.2. and 6.3.) show the change from baseline in FEV1, FVC and mean PEF in individual patients after treatment with inhaled beclomethasone. These show a unimodal distribution of change in each parameter after treatment with inhaled beclomethasone.



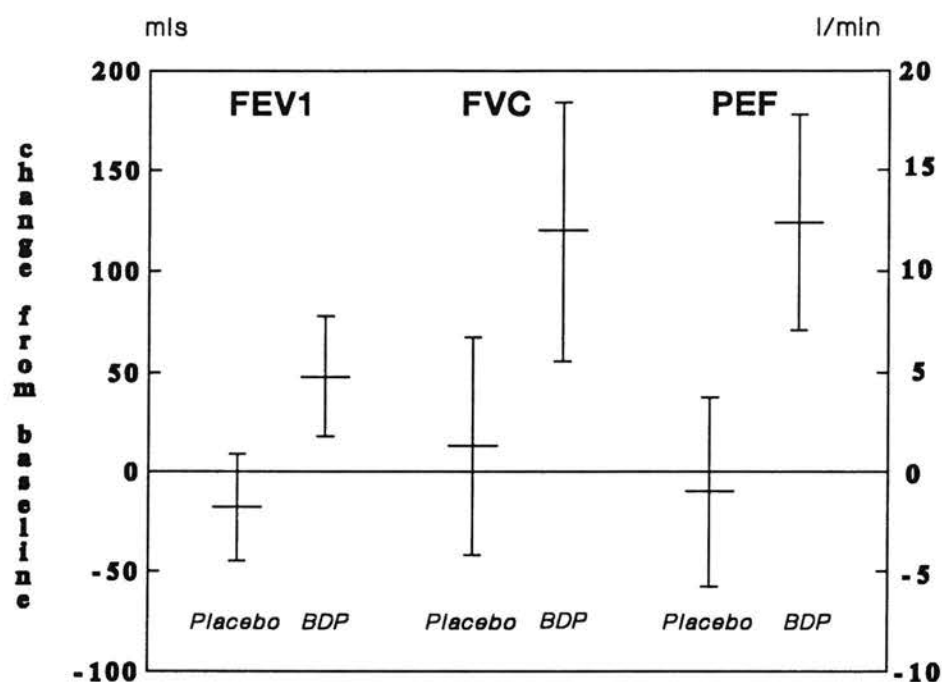


Figure 6.1. Error bar plot showing the change from baseline values in FEV1, FVC, and mean PEF after placebo or inhaled beclomethasone (BDP). The error bars represent the mean (and 95% confidence intervals for the mean) of the differences. For FEV1 and FVC differences the left axis shows the values, for mean PEF the right hand axis.

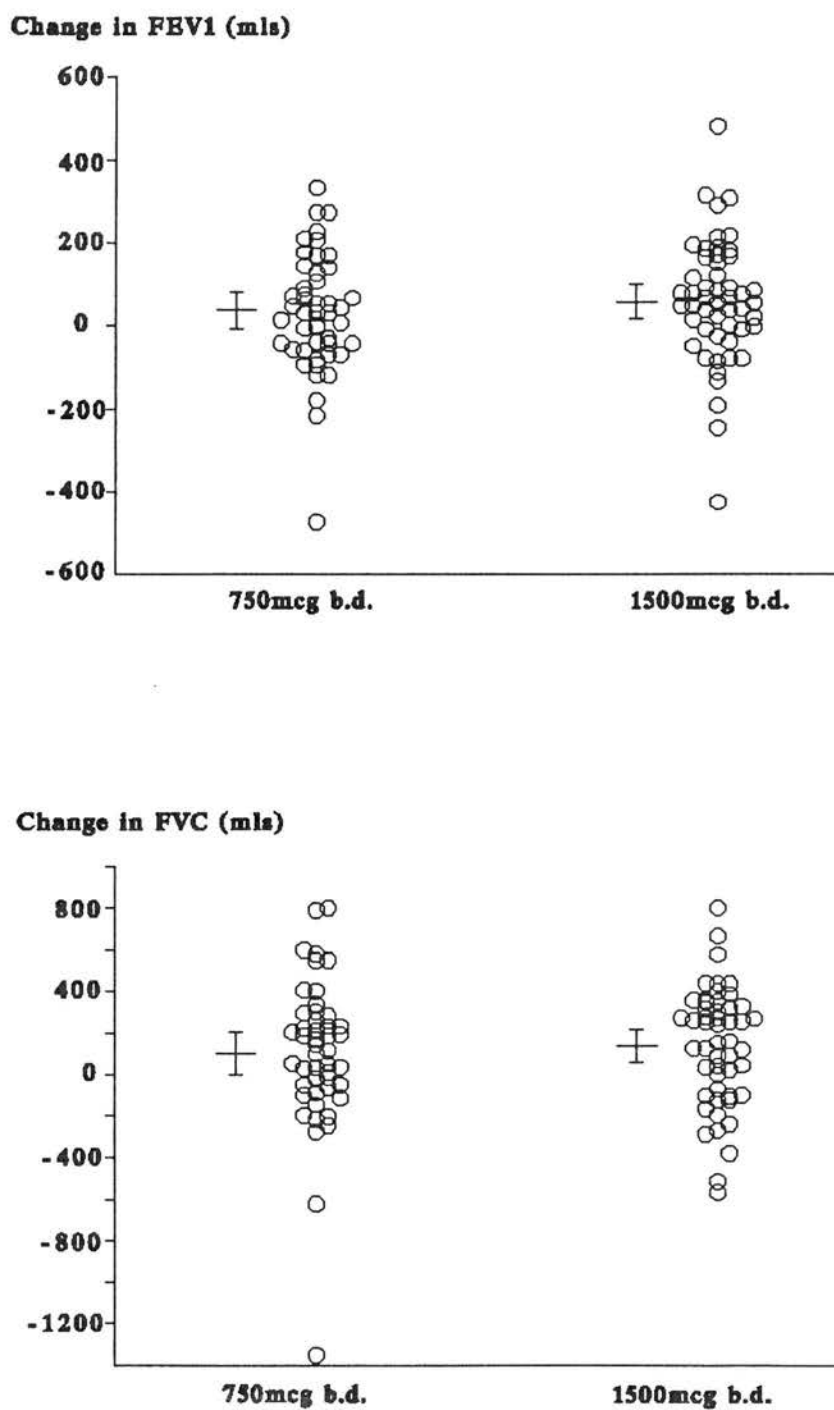


Figure 6.2. Scatterplots of change from baseline in FEV1 and FVC after inhaled beclomethasone for the two dose groups. Error bars show mean and 95% confidence intervals for the mean of the difference.

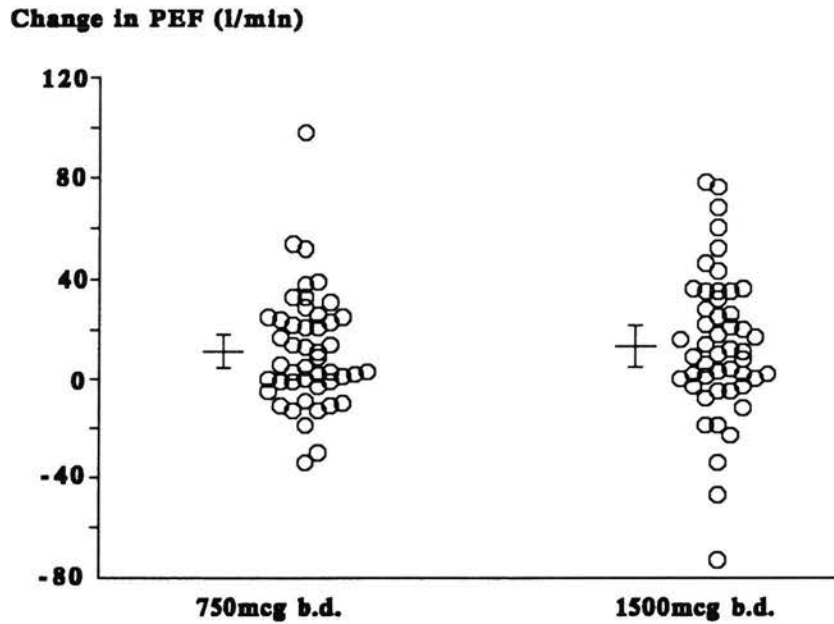


Figure 6.3. Scatterplot of change from baseline in mean PEF after inhaled beclomethasone for the two dose groups. Error bars show mean and 95% confidence intervals for the mean of the difference.

Further analysis was undertaken to answer the question - do responders to inhaled beclomethasone show an increased effect of the higher dose of BDP? It would not be surprising to find no detectable differences in the effect on lung function of the two doses of inhaled beclomethasone when the majority of patients show no response to treatment on an individual level. The lack of effect of treatment in non responders may mask a greater effect of the higher dose on responders to treatment.

The difference between placebo and inhaled beclomethasone values was compared for the two dose groups by an unpaired Student *t* test, for FEV1 in patients who showed a change in FEV1 of greater than 180ml, for FVC in patients showing a change in FVC greater than 300ml, and for mean PEF in patients where the mean PEF improved by at least 15 l/min. No significant differences were found (table 6.4.).

Table 6.4. Mean (95% confidence limits) for the difference between placebo and inhaled beclomethasone values for FEV1, FVC and mean PEF in patients showing large improvements in these variables (see text).

	BDP dose	
	750mcg b.d.	1500mcg b.d.
FEV1 (litres)	290 (170 to 410) n=5	320 (257 to 382) n=11
FVC (litres)	588 (383 to 792) n=9	508 (401 to 615) n=15
mean PEF (l/min)	28 (18 to 37) n=12	36 (29 to 43) n=21

No significant differences.

*c. The effect of inhaled beclomethasone on post bronchodilator spirometry and other measures of lung function.*

The effect of inhaled beclomethasone on the post bronchodilator FEV1 and FVC was also examined, although this was not a primary end point of the trial. It was possible that the results of reversibility tests would be affected by measurement of bronchial hyperresponsiveness to inhaled histamine immediately prior to the bronchodilator test. Therefore an initial analysis compared the absolute change in FEV1 after both salbutamol and ipratropium bromide, measured during the baseline period, in patients who had bronchial hyperresponsiveness measured immediately prior to reversibility testing (group 1) and those who did not have this test performed (group 2). This showed no effect of a prior histamine test on reversibility to either drug. The change in FEV1 following salbutamol was (as mean [95% confidence interval])

group 1, 150 [114 to 186]ml, group 2, 142 [108 to 176] ml, following ipratropium bromide, group 1, 93 [59 to 127]ml, group 2, 141 [101 to 182]ml. As no significant effect of a prior histamine inhalation test was detected, the post bronchodilator FEV1 and FVC data was analysed ignoring this difference in protocol.

After the baseline period 49 of the 98 patients who completed the inhaled beclomethasone phase had reversibility of FEV1 and FVC measured to salbutamol, the remainder to ipratropium bromide. To look at the effect of inhaled beclomethasone on post bronchodilator spirometry the change from the post bronchodilator value at the end of the placebo phase was compared in patients for the two inhaled beclomethasone dosage groups. An unpaired Student *t* test was used for this comparison, and the test performed independently in patients who received salbutamol as the bronchodilating drug, and in the patients in whom ipratropium bromide was used.

Forty nine patients had FEV1 and FVC measured after salbutamol after both placebo treatment, and active treatment with inhaled beclomethasone. 26 patients received the higher dose of inhaled beclomethasone, the remainder 750mcg b.d.. In patients taking 1500mcg b.d. BDP, the post salbutamol FEV1 was a mean (95% CI) of 93.5 (26.7 to 160)ml higher at the end of the inhaled beclomethasone treatment phase when compared to the value seen after placebo. For post salbutamol FVC the value was a mean of 118 (12.6 to 223)ml higher after inhaled beclomethasone. In the lower BDP dose group the post salbutamol FEV1 and FVC did not change significantly, for FEV1 the difference from placebo was -3.9 (-55 to 47)ml, for FVC -17.4 (-114 to 78.9)ml. The higher dose had a significantly greater effect on post bronchodilator FEV1 ( $p < 0.03$ ), but the difference between the effect of the two doses on post bronchodilator FVC just failed to reach conventional levels of statistical significance ( $p = 0.058$ ).

In the remaining patients in whom post bronchodilator spirometry was measured after ipratropium bromide, only the post bronchodilator FEV1 in the 1500mcg b.d. BDP dose group showed a

significant improvement following inhaled beclomethasone ( mean change in FEV1 91.6 [21.1 to 162]ml). In the 750mcg b.d. group the mean change in FEV1 was 3.5 (-66 to 73)ml, the mean change in FVC was 39.6 (-17.9 to 100)ml. The mean change in post bronchodilator FVC for the patients treated with 1500mcg b.d. inhaled beclomethasone was 29.6 (-79 to 139)ml. The effect of the two doses on post ipratropium bromide spirometry was not significantly different. The mean post bronchodilator FEV1 and FVC after placebo and inhaled beclomethasone are shown in table 6.5..

There was no significant effect of placebo or inhaled beclomethasone on gas transfer measurements. At baseline the mean (SEM) carbon monoxide gas transfer for the whole lung (TLCO) was 5.38 (0.23) mmol/min/kPa, the volume corrected value was 1.03 (0.04) mmol/min/kPa/l. After placebo the respective values were 5.37 (0.24) mmol/min/kPa, and 1.02 (0.04) mmol/min/kPa/l, after inhaled beclomethasone 5.49 (0.24) mmol/min/kPa and 1.03 (0.04) mmol/min/kPa/l.

Table 6.5. The mean (SEM) post bronchodilator FEV1 and FVC at the end of the placebo and BDP treatment phases, for patients receiving salbutamol and ipratropium bromide as the bronchodilator.

	Placebo	BDP
<i>1. Salbutamol</i>		
<i>FEV1 (litres)</i>		
750mcg b.d.	1.25 (0.10)	1.24 (0.10)
1500mcg b.d.	1.15 (0.09)	1.25 (0.09)
<i>FVC (litres)</i>		
750mcg b.d.	3.02 (0.16)	3.00 (0.16)
1500mcg b.d.	3.10 (0.19)	3.22 (0.19)
<i>2. Ipratropium bromide.</i>		
<i>FEV1 (litres)</i>		
750mcg b.d.	1.16 (0.08)	1.15 (0.08)
1500mcg b.d.	1.10 (0.10)	1.19 (0.11)
<i>FVC (litres)</i>		
750mcg b.d.	2.85 (0.16)	2.78 (0.15)
1500mcg b.d.	3.00 (0.15)	3.03 (0.14)



*d. Response to inhaled beclomethasone in individual patients.*

To assess response to treatment in individual patients the response rate to the two doses of inhaled beclomethasone was compared. In the patients receiving 750mcg b.d. 16/47 (34%) showed a response, in the 1500mcg b.d. group 17/51 (33%) responded (Chi squared=0.06,ns). To assess the efficacy of inhaled beclomethasone against placebo both beclomethasone dose groups were therefore combined.

In individual patients a response to placebo therapy occurred in 15 patients (15%), but in 33 patients after inhaled beclomethasone (34%). The difference in response rates was statistically significant (table 6.6.).

Figure 6.4. shows the measures in which a response was noted. In 27 patients the response was seen in only one of the three primary end points, in two measures in 4 cases and in all three measures in the remaining two responses.

For patients showing a response in a measure the distribution of absolute change is shown in figure 6.5. for FEV1 (18 cases), FVC (12 cases) and PEF (11 cases).

In the 18 patients showing a response in FEV1 the mean (95% CI) change in FVC was 14.6 (10.2 to 19.1)%, in mean PEF 10.5 (3.4 to 17.6)%. Only 2 of the 18 patients failed to show an improvement in FVC or mean PEF of at least 10%. In the 12 FVC responders the change in FEV1 was 18.9 (10.9 to 26.8)%, and 9.2 (-0.6 to 19.1)% in mean PEF. In 9 of these 12 FVC responders the change in FEV1 or mean PEF exceeded 10%. For the 11 patients showing a response in PEF the changes in FEV1 and FVC were 10.6 (-0.5 to 21.1)% and 2.8 (-7.9 to 13.5)% respectively, but 4 of these patients failed to show an improvement in FEV1 or FVC of at least 10%.

Table 6.6. Response to inhaled beclomethasone and placebo in individual patients.

Placebo	Beclomethasone	
	Responder	Non responder
	22 11	4 61

McNemar test  $p < 0.001$

**BDP Responses**

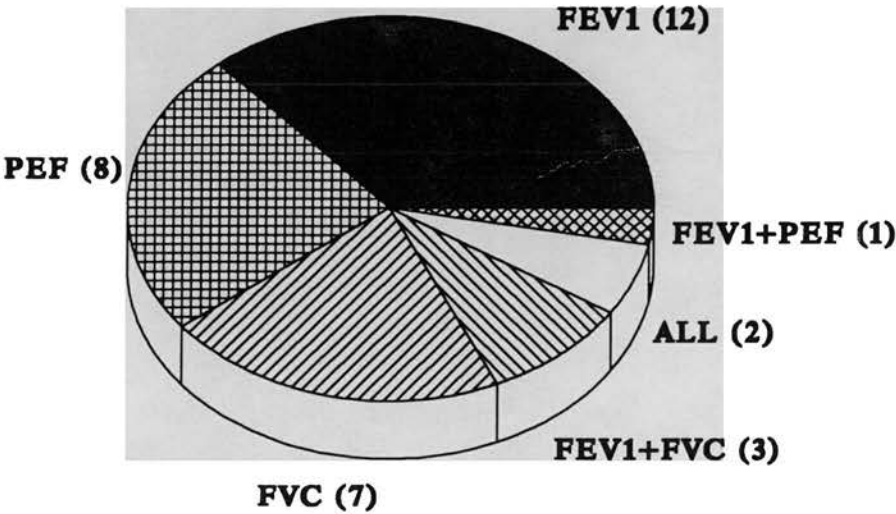


Figure 6.4. Pie chart illustrating the measure or measures in which a response was seen in individual patients.

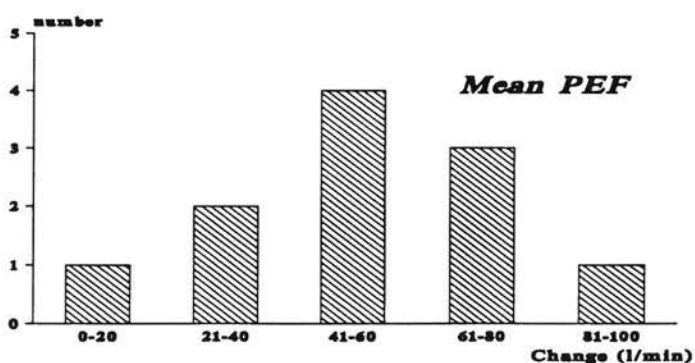
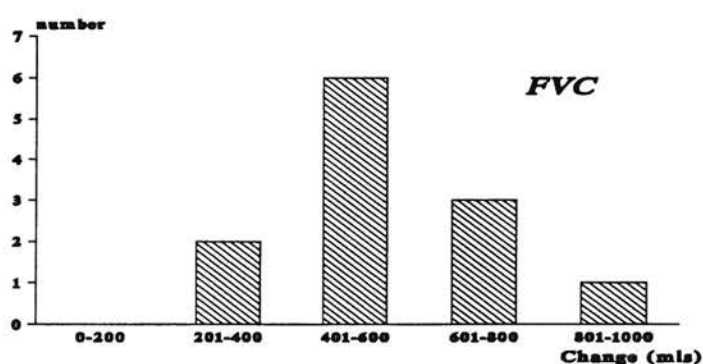
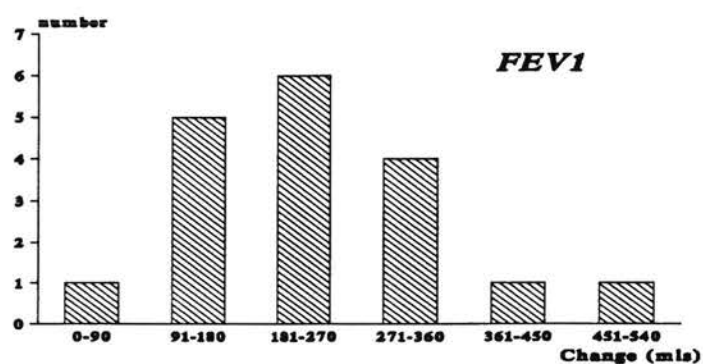


Figure 6.5. Distribution histograms of the absolute change in each measure, in patients classified as showing a response to treatment in that measure.

### 6.2.2. The effect of oral prednisolone.

#### *a. Characteristics of the two final phase treatment groups.*

The characteristics of the patients who received oral prednisolone 40mg per day for the final treatment phase, and the smaller number who continued on inhaled beclomethasone are given in table 6.7.. The two treatment groups were well matched in terms of most of the likely confounding factors. The patients receiving oral prednisolone showed a higher mean level for the serum IgE, but similar levels of skin test reactivity.

#### *b. The effect of oral prednisolone on FEV1, FVC and mean PEF.*

There was no significant difference in the change in FEV1 or mean PEF from that recorded at the end of the second (inhaled beclomethasone) treatment phase, between the two groups. Those receiving prednisolone showed a small mean (95% CI) fall in FEV1 of 19 (-59 to 20)ml, the 31 patients continuing on inhaled beclomethasone alone showed a mean fall of 26 (-69 to 18)ml. The change in mean PEF was 3.1 l/min (-1.6 to 7.8) for the prednisolone group, 2.8 l/min (-6.0 to 11.6) for the inhaled beclomethasone group. The patients continuing on inhaled beclomethasone alone showed a larger fall in FVC during the third treatment phase although the difference was not statistically significant, oral prednisolone -5.0 (-94 to 84)ml, inhaled beclomethasone -98 (-208 to 11)ml. The changes in each parameter are shown as an error bar plot in figure 6.6., and as scatterplots for each variable in figure 6.7., and 6.8..

When the post bronchodilator FEV1 and FVC were examined no difference in the change in this value during the third phase of treatment was seen between patients receiving oral prednisolone and those continuing on inhaled beclomethasone [mean (95% CI) change; FEV1 prednisolone group 23(-23 to 69)ml, beclomethasone alone group -25(-69 to 20)ml; FVC prednisolone group 53(-56 to 111)ml, beclomethasone alone group -9(-116 to 98)ml.

Table 6.7. Baseline characteristics of the two final treatment phase groups. As mean (SEM) unless indicated.

	Treatment group	
	Prednisolone +BDP (n=61)	BDP alone (n=31)
Females (number)	20	5
Age (years)	66 (0.8)	66 (1.2)
FEV1 (litres)	1.08 (0.08)	1.05 (0.06)
FEV1 (% predicted)	41.1 (2.0)	39.1 (2.7)
FEV1/FVC %	39.4 (1.6)	39.0 (2.2)
mean PEF (l/min)	230 (12)	248 (17)
TLCO (% predicted)	69.4 (3.2)	67.2 (5.5)
KCO (% predicted)	59.3 (2.7)	57.2 (4.8)
diurnal variation in PEF(% predicted)	11.5 (0.8)	9.9 (1.0)
FEV1 reversibility to 200mcg salbutamol as % predicted FEV1	5.8 (0.7)	5.6 (1.0)
Serum IgE (ku/l) (geometric mean)	86	54 *
Number with positive skin test (%)	11 (18)	7 (22)
Smoking status [as number (%)]		
Current smokers	26 (42)	15 (48)
Ex smokers	34 (56)	16 (42)
Never smokers	1 (2)	0
Cigarette consumption (pack years)	47 (4.4)	49 (4.7)

\* p < 0.05, all other comparisons non significant.

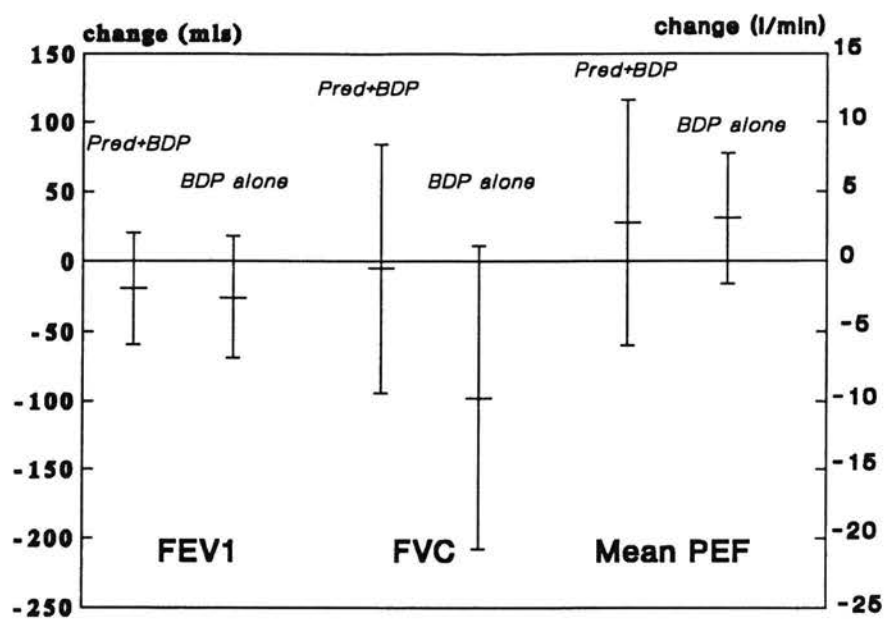


Figure 6.6. Error bar plot showing the mean change in FEV1, FVC, and mean PEF during the final active treatment phase. The error bars show the mean and 95% confidence intervals for the mean of the differences.

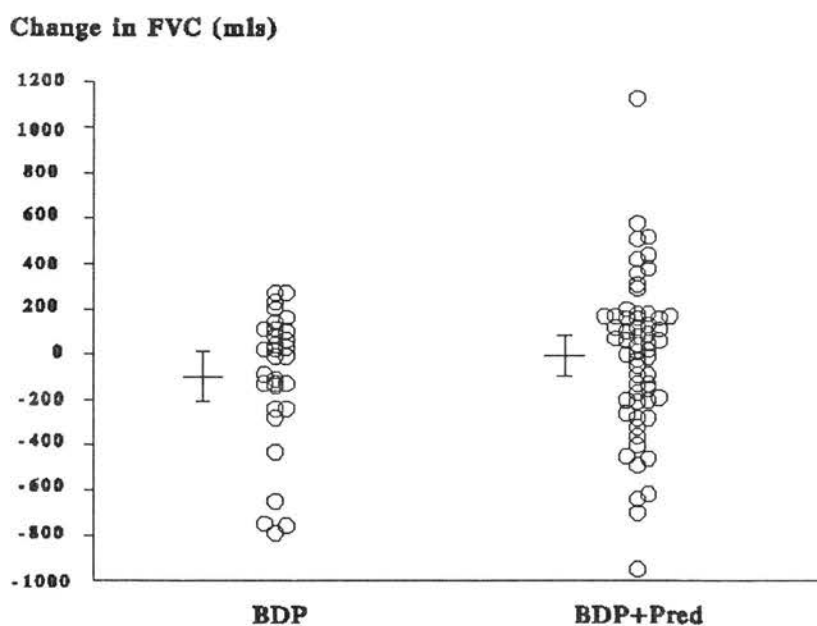
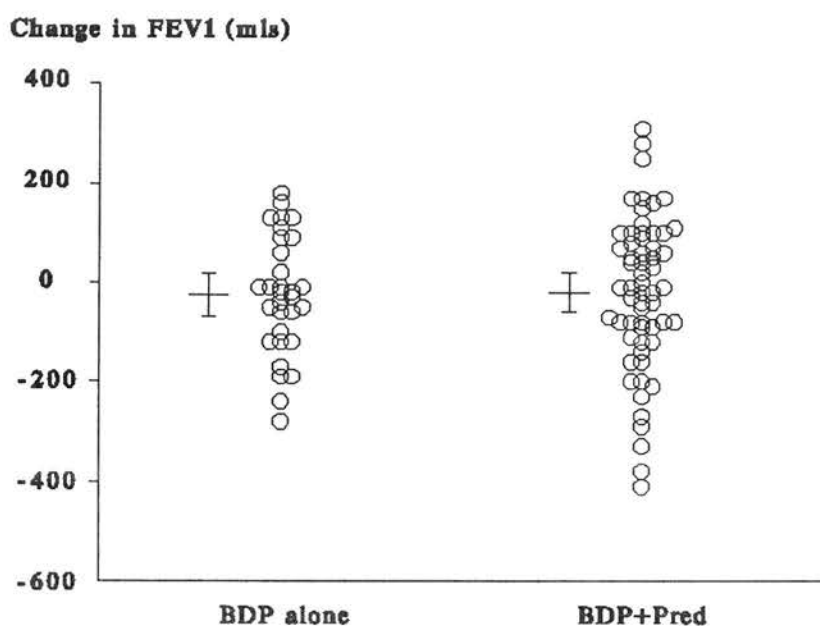


Figure 6.7. Scatterplots of the change in FEV1 and FVC during the final treatment phase in individual patients for the two treatment groups. The error bars show the mean and 95% confidence intervals for the mean of the difference.



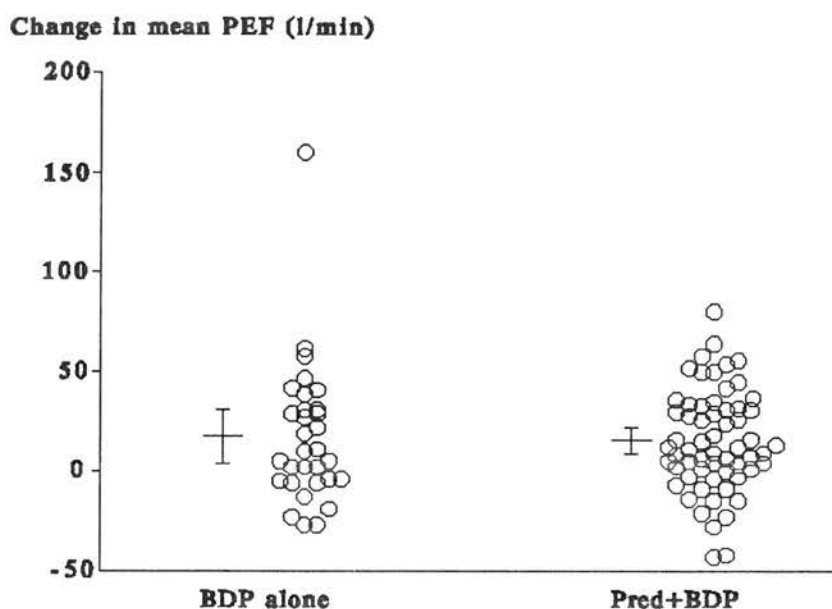


Figure 6.8. Scatterplot of the change in mean PEF during the final treatment phase in individual patients for the two treatment groups. Error bars show the mean and 95% confidence intervals for the mean of the difference.

Table 6.8. Response to inhaled beclomethasone and combined treatment with oral prednisolone and inhaled beclomethasone in individual patients receiving combined treatment during the final treatment phase.

Beclomethasone alone	Beclomethasone + Prednisolone	
	Responder	Non responder
Responder	11	5
Non responder	8	37

McNemar test non significant.

*c. Response to final phase treatment in individual patients.*

The categorical analysis showed that after the final treatment phase the response rate, defined with respect to baseline values, was similar in the two treatment groups. Of the patients receiving oral prednisolone in addition to inhaled beclomethasone 19 (31%) showed a response to the combined final treatment (when compared to baseline values), whilst 10 (32%) of the inhaled beclomethasone alone group showed a response as defined (chi squared=0.01; DF=1;ns). The response category to both the second (inhaled beclomethasone) and final treatment phases of the 61 patients who received oral prednisolone and inhaled beclomethasone during the final stage is shown in table 6.8.. By the McNemar test the difference in response rate was not statistically significant.

Figure 6.9. shows the measure in which a response was noted for the two final phase treatment groups. In the combined treatment group 11 responses occurred in only one measure, 6 in two, and two in all three measures used to define response. In the group receiving inhaled beclomethasone alone 7 responses were seen in one measure only, the remaining three responders showing a greater than 20% response in two of the parameters. For patients classified as a responder to a particular measure after the final treatment phase, the distribution of the absolute change in that measure is shown in figure 6.10.. Individuals from each of the two treatment groups are indicated.

In the 18 patients showing a response after either of the final treatments in FEV1 the mean (95% CI) change in FVC was 19.9 (15 to 24.8)% and 12.9 (4.2 to 21.6)% in mean PEF. In all 18 FEV1 responders the FVC or mean PEF improved by at least 10%. For the 9 patients showing a response after the final treatment phase in FVC the change in FEV1 was 28.7 (12.5 to 44.9)% and 11 (-1.6 to 23.6)% in mean PEF, with 7 patients improving in either FEV1 or mean PEF by at least 10%. The 15 PEF responders showed a change in FEV1 and FVC of 15 (4.1 to 25.3)% and 11.8 (3.7 to 19.8)% respectively. Eleven of the 15 PEF responders showed an improvement in FEV1 or FVC of at least 10%.

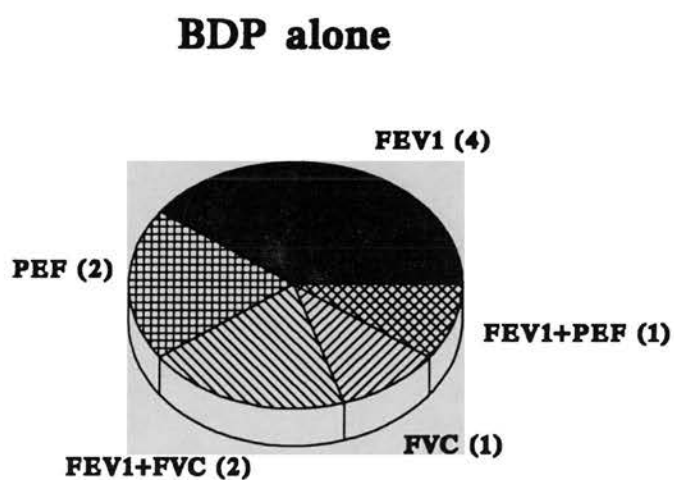
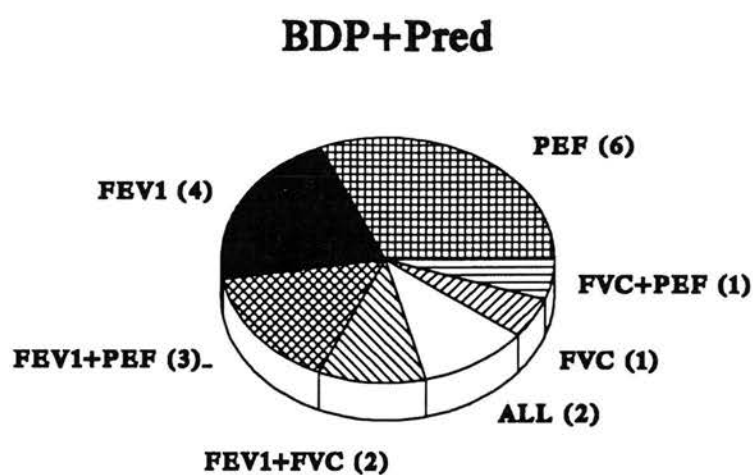


Figure 6.9. Pie chart illustrating the measure or measures in which a response was seen in individual patients for the two final treatment groups.

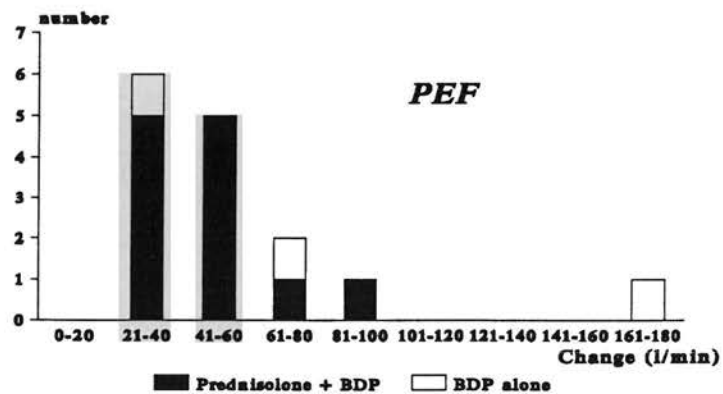
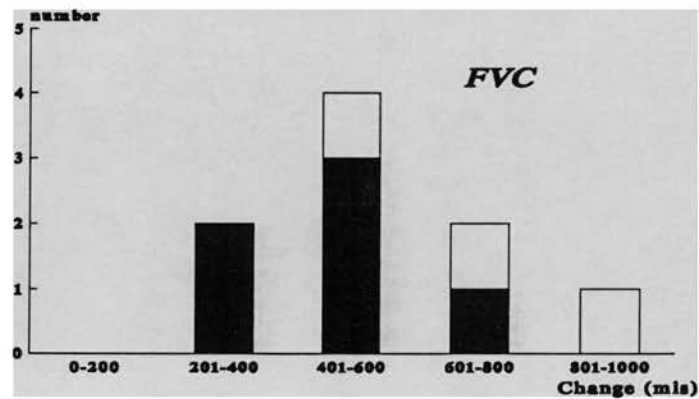
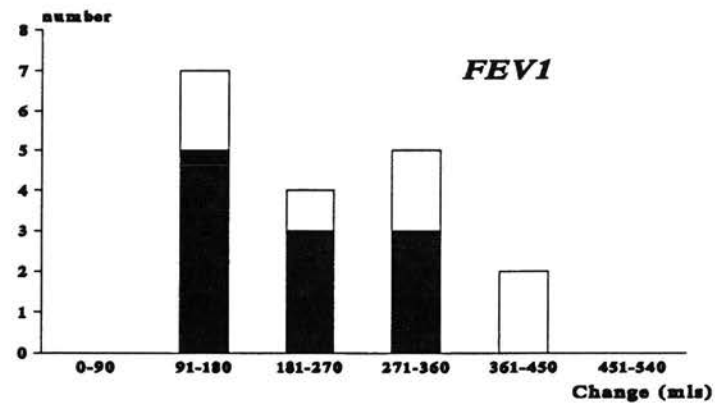


Figure 6.10. Distribution histograms of the absolute change in each measure after the final treatment phase, in responders in that measure.

### 6.3. DISCUSSION.

The results have shown that inhaled beclomethasone dipropionate is effective in producing improvement in physiological parameters in patients with chronic airflow obstruction. Both in a 'group' analysis and a 'categorical' analysis inhaled beclomethasone was more effective than placebo in improving pre bronchodilator FEV1 and FVC on the final day of treatment, and mean PEF over the final seven days of the treatment period. The analysis detected no difference between the two doses of inhaled beclomethasone used in producing improvement in the parameters used as a primary end point. The categorical response in both doses was virtually identical with just over 33% of patients showing a response to treatment as defined. However when post salbutamol FEV1 and FVC were analysed there seemed to be a greater effect of the higher dose of BDP on these secondary end points.

When oral prednisolone was added during the final active treatment phase to two thirds of the patients no significant improvement was noted when the changes over the final treatment phase in each of the primary end points were compared to that seen in the one third of patients who continued on inhaled beclomethasone alone. The results did show a larger fall in FVC in the group on inhaled beclomethasone, but this failed to reach statistical significance. At the end of the final treatment phase a similar proportion of patients responded to continued treatment with inhaled beclomethasone alone (32%) as did to combined treatment with oral prednisolone and inhaled beclomethasone (31%). When the 61 patients who received combined therapy as the final treatment phase were analysed alone, the response rate to inhaled beclomethasone at the end of the second treatment phase was similar to that seen at the end of the final treatment phase. Hence, both a 'group' and a 'categorical' analysis showed no further beneficial effect of oral prednisolone in this group of patients over 3 weeks.

The absolute changes from baseline in the three end points

after inhaled beclomethasone were small. This reflects the fact that nearly two thirds of the patients were unresponsive, as defined, to three weeks treatment with the drug. The effect of this is to reduce the overall mean change in each of the parameters when the group is considered as a whole. The mean improvement in FEV1 after inhaled beclomethasone is within the 95% confidence limits of the improvement in FEV1 seen after oral prednisolone in similar patients in two previous trials(83,87). Two further studies reported significant effects of oral prednisolone which were about three times that seen after inhaled beclomethasone in this study(88,90).

Although the mean change is small, when patients who show a change in FEV1 and FVC which is greater than the short term variability in these end points are examined(94), the mean change in FEV1 in these patients is approximately 25% of the mean baseline FEV1, and the change in FVC seen approximately 20% of the mean FVC of the patients studied (table 6.4.). Changes of this degree are undoubtedly of clinical significance.

Criticism may be levelled at the design of the study. A sequential design with all patients receiving placebo as the initial treatment followed by two active treatment periods was chosen because of our own work showing that the beneficial effects of corticosteroids on PEF may last for well over 2 weeks after the drugs had been withdrawn(78). Indeed further unpublished analysis of this work suggests that oral prednisolone may have effects lasting for up to 6 weeks after withdrawal of the drug. Hence, in any double blind cross over trial the washout period should be 4 to 6 weeks in order to eliminate any carry over effect of active treatment on the following treatment phase. With a three week treatment phase this would have entailed a trial of approximately 6 months. This was felt to be impracticable, and the low drop-out rate seen in this study would have been much more exaggerated if such a design had been followed.

The patients were unaware of the sequential nature of the trial, and each treatment given appeared identical. The dose allocation, and allocation to the final treatment phase group was

made on a double blind basis. Strict objective criteria were used for the measurement of lung function, hence any unintentional bias introduced because of trial design is likely to have been small. The comparisons between the two beclomethasone dose groups, and between the two treatment groups in the final phase are statistically 'pure' as effectively this comparison was done on a double blind basis.

The response rate to both inhaled beclomethasone alone, and combined treatment with inhaled beclomethasone and oral prednisolone was just over 30%. This compares favorably to response rates reported in the literature and reviewed in the introduction. These show quite marked variability, between 6 and 56% of patients showing a response to oral prednisolone. Part of the variability may be explained by differences in trial design and patient selection. The response rate seen in this study is at the upper end of that quoted in published papers, as was the response rate seen in our previous study(95). This probably reflects the choice of three end points to determine response, In the majority of previous studies only 1 or possibly 2 objective measures of lung function have been used to judge response. In particular, very few trials have used domiciliary PEF monitoring as an objective measure of treatment effect. Mitchell et al found that of 13 patients showing a response to treatment with oral prednisolone in mean PEF 6 responded in FEV1, and only 5 in FVC(93). They concluded that domiciliary PEF monitoring was the most sensitive of the three parameters. If this had been omitted from our study design then 8/33 responses would have been missed. The placebo response rate in this study is again similar to that seen in the published literature (10-40%).

Comparison of the results in the present study to that to inhaled corticosteroids in published studies is difficult because of the shortcomings of the published work. Harding & Freeman and Wardman et al, studied only small numbers of patients(100,102). In Wardman's studies it appeared that all patients who responded to inhaled beclomethasone also showed a response to oral prednisolone. Oral prednisolone produced a slightly greater response in the patients classified as responders but no group effect



of either inhaled beclomethasone or oral prednisolone was seen. The changes in FEV1, FVC and mean PEF seen in this study in the responders was large, suggesting undiagnosed asthmatics may have inadvertently been included.

In the study of Williams and Shim interpretation is extremely difficult as all patients continued on a small dose of oral prednisolone and the dose of inhaled beclomethasone used was very small(101). This may explain the fact that inhaled beclomethasone only produced a categorical response in 50% of the patients who responded to prednisolone. Our own previous study suggested that response to inhaled beclomethasone occurred in about half as many patients as a response to oral prednisolone(95). Forty-two percent of patients responded to oral prednisolone whereas only 24% responded to inhaled beclomethasone.

The response rate to beclomethasone in this earlier study is less than that seen in the current study. One of the major differences between the previous study and the current investigation is in the mode of delivery of drug. Spacing devices (Volumatic) were used by all patients in the current study, to ensure optimal delivery of the inhaled drug to the airways, whereas the earlier trial used a metered dose inhaler alone. It is possible that the difference in response rate to inhaled beclomethasone between the two studies, and the difference in response to inhaled beclomethasone and oral prednisolone seen in the previous study was due primarily to poor deposition of the inhaled drug in the earlier study. The results of the current study would support this suggestion. When drug delivery was optimized by use of a spacing device, no difference was seen between the effect of the two doses of inhaled beclomethasone, neither was any additional effect of oral prednisolone noted. If this is the reason for the disparate results then by implication the dose response characteristics for inhaled beclomethasone shows a plateau above a dose of 1500mcg per day.

Another possible explanation for the difference in response rates between the two studies may be the longer duration of treatment used in the current study. Our previous analysis suggested

that up to 20% of responders may not have reached the peak response at two weeks(78). The extra weeks treatment used in the current study may account for the higher response rate to inhaled beclomethasone.

The slightly lower response rate overall in the current study may be explained by differences in the patients studied. The population in the previous study had more life long non smokers, more patients with positive skin tests, and the serum IgE level was higher (see table 10.10.). In other studies response to corticosteroids is at least partially related to the atopic characteristics of the patients studied(69,71).

Defining response in terms of percentage change in a variable risks selecting responders from patients with low values of the variable chosen(85). Small changes which may be within the measurement error of the variable used to define response assume undue significance when the starting level of that variable is low. In the present study 6 of the 18 responses seen in FEV1 were within the short term variability limit quoted by Tweeddale et al(94), although only 1 of the FVC responses to inhaled beclomethasone had a change in absolute terms within the short term variability of this measure. There is no data available to judge the significance of the absolute changes in mean peak flow seen. Redefining response to exclude patients with percentage changes which fulfil the criteria, but with small absolute changes within the short term variability of the measures as suggested by others(73), does not alter the conclusions of the study significantly. Although the overall response rate to inhaled beclomethasone and oral prednisolone is reduced slightly, inhaled beclomethasone at both doses used is still more effective than placebo in producing response , there is no difference between the two doses of inhaled beclomethasone and the addition of oral prednisolone does not improve the response rate over that seen to inhaled beclomethasone alone.

The role of asthmatic features in determining response to inhaled and oral corticosteroids will be investigated later in the thesis.

## **7. THE EFFECT ON SYMPTOMS AND QUALITY OF LIFE.**

### **7.1. ANALYSIS.**

The effect of placebo, and the two doses of inhaled beclomethasone on the scores derived from the quality of life questionnaire(167), diary card breathlessness scores and the results of the oxygen cost diagram were assessed by a repeated measures analysis of variance, with dose of drug entered as a factor. Where significant effects were detected a Fisher's LSD test was used to determine which comparisons were significant. The effect of treatment on subjective measures was also analysed in patients classified as responders to treatment on the basis of changes in objective lung function tests.

To analyse the effect of adding oral prednisolone to the inhaled drug during the third and final treatment phase, the change in each subjective measures from the previous phase was compared between the two thirds of patients who received oral prednisolone and inhaled beclomethasone, and the remaining third who continued on inhaled beclomethasone alone. An unpaired Student *t* test was used for this part of the analysis.

Correlations between measures of lung function and the subjective measures at baseline were assessed by Pearson's correlation coefficient. Likewise associations between changes in lung function variables and subjective measures after treatment with inhaled beclomethasone were assessed by calculation of the Pearson correlation coefficient.

The quality of life questionnaire dyspnea element requires the patient to identify 5 activities of daily living which induce breathlessness. In patients who were unable to identify five activities, the dyspnea score was standardised by dividing the total dyspnea score by the number of activities, and multiplying by five. For the dyspnea score of the quality of life questionnaire high scores indicate less breathlessness, higher scores with the oxygen cost diagram also indicate less breathlessness, whereas diary card breathlessness scores are lower the less breathless the patient feels.

The quality of life questionnaire measures physical and emotional function. The physical function element consists of the responses to the dyspnea and fatigue components. A subjective response to treatment was defined in terms of response in physical function, as an improvement in the combined dyspnea and fatigue scores of at least 4 compared to baseline(187). The number of subjective responders in each of the inhaled beclomethasone dose groups was compared by a chi square test, and comparison of the subjective response to placebo and inhaled beclomethasone by McNemar test. Changes in objective lung function measures after inhaled beclomethasone in the two subjective response groups were compared by an unpaired Student *t* test.

## 7.2. RESULTS.

### 7.2.1. The relation between Quality of Life and baseline lung function variables.

Correlations between spirometric variables, lung volumes, carbon monoxide gas transfer and diurnal variation in PEF and subjective measures of dyspnea are given in table 7.1.. The dyspnea score from the quality of life questionnaire correlated poorly with all objective measures of lung function, whereas the results of the oxygen cost diagram, and the diary card breathlessness score showed stronger correlations with spirometric measures and carbon monoxide gas transfer.

Table 7.1. Pearson correlation coefficients for the association between subjective measures of breathlessness used and various measures of lung function.

	Dyspnea	SOB	O2cost
FEV1	0.08	-0.34**	0.45***
FVC	0.06	-0.16	0.18
mean PEF	0.14	-0.36***	0.37***
diurnal variation in PEF (% mean)	0.13	-0.21*	0.17
TLC	-0.05	-0.01	-0.08
FRC	-0.11	0.09	-0.22*
RV	-0.14	0.12	-0.22*
TLCO	0.16	-0.59***	0.55***
logPD20	0.13	-0.14	0.11
Pimax	0.12	-0.23*	0.19
Pemax	0.13	-0.15	0.14

Dyspnea - quality of life questionnaire dyspnea score  
SOB - diary card breathlessness score  
O2cost - oxygen cost diagram score

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

### **7.2.2. The effect of inhaled beclomethasone.**

A small but significant improvement in the dyspnea score from the quality of life questionnaire was seen after treatment with inhaled beclomethasone. No difference between the two doses given was detected. Placebo therapy also improved this measure significantly over the baseline score, but treatment with inhaled beclomethasone caused a further small but statistically significant increase (table 7.2.).

The three non respiratory components of the quality of life questionnaire showed variable changes. Only the 'mastery' questions showed a significant improvement after inhaled beclomethasone when compared to both placebo and baseline answers. The 'fatigue' element of the questionnaire showed a significant difference between placebo scores and those recorded after inhaled beclomethasone, but no difference between baseline and active treatment. The answers to the 'emotional function' questions improved after both placebo and active therapy, but only the difference between responses at baseline and after inhaled beclomethasone was statistically significant. This element also showed a significant dose treatment interaction, with the lower dose having more effect. All other analyses revealed no significant difference between the effect of the two doses of inhaled beclomethasone given. The change in the scores for all four dimensions of the quality of life questionnaire from that after placebo to that after inhaled beclomethasone are shown in figure 7.1..

The results of the oxygen cost diagram showed a significant improvement over baseline with both placebo and inhaled beclomethasone, but no difference between the active drug and placebo therapy. However diary card breathlessness scores fell with inhaled beclomethasone but showed a small rise from baseline values after placebo. Both doses of inhaled beclomethasone were as effective at improving this measure (table 7.3.).

Table 7.2. The mean (SEM) scores for the components of the quality of life questionnaire at baseline, and after treatment with placebo and inhaled beclomethasone.

	Baseline	Placebo	BDP
Dyspnea			
750mcg b.d.	18.0 (0.8)	19.0 (0.9)	20.4 (1.0)
1500mcg b.d.	17.7 (0.7)	19.4 (0.9)	21.3 (1.0)
Treatment effect F-ratio=24.96, DF=2,91 $p < 0.0001$			
Interaction F-ratio=0.92, DF=2,91 ns.			
Fatigue			
750mcg b.d.	17.6 (0.7)	17.8 (0.7)	18.8 (0.8)
1500mcg b.d.	17.4 (0.8)	16.9 (0.7)	17.3 (0.8)
Treatment effect F-ratio=3.61, DF=2,94 $p < 0.03$ .			
Interaction F-ratio=2.76 DF=2,94 ns.			
Emotional Function			
750mcg b.d.	33.4 (1.2)	35.1 (1.2)	36.6 (1.2)
1500mcg b.d.	32.8 (1.3)	33.1 (1.3)	32.9 (1.5)
Treatment effect F-ratio=4.89, DF=2,94 $p < 0.01$			
Interaction F-ratio=4.2, DF=2,94 $p < 0.02$			
Mastery			
750mcg b.d.	19.7 (0.9)	20.1 (0.8)	20.3 (0.9)
1500mcg b.d.	20.0 (0.8)	20.9 (0.8)	21.8 (0.8)
Treatment effect F-ratio=9.25, DF=2,94 $p < 0.0001$ .			
Interaction F-ratio=2.75, DF=2,94 ns.			



Table 7.3. The mean (SEM) scores for the oxygen cost diagram (O2cost), and diary card breathlessness score (SOB), at baseline and after placebo and inhaled beclomethasone.

	Baseline	Placebo	BDP
O2cost			
750mcg b.d.	121 (5.5)	127 (6.2)	124 (5.5)
1500mcg b.d.	118 (5.4)	124 (5.4)	130 (5.8)
Treatment effect F-ratio=5.8, DF=2,89 $p < 0.005$ .			
Interaction F-ratio=2.34, DF=2,89 ns.			
SOB			
750mcg b.d.	3.1 (0.2)	3.2 (0.2)	2.9 (0.2)
1500mcg b.d.	2.8 (0.2)	3.0 (0.2)	2.6 (0.2)
Treatment effect F-ratio=9.52, DF=2,88 $p < 0.00002$ .			
Interaction F-ratio=0.31, DF=2,88 ns.			

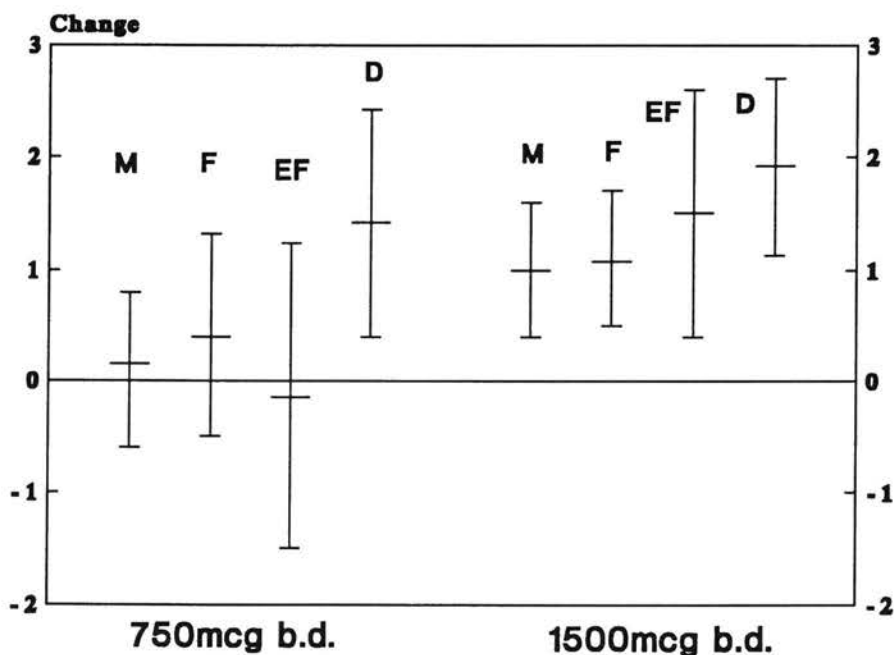


Figure 7.1. The change from placebo scores in the four dimensions of the quality of life questionnaire, for the two BDP dose groups. M=mastery, F=fatigue, EF=emotional function, D=dyspnea. Error bars show mean and 95 % confidence intervals for the mean of the difference.

The correlation between the change in FEV1, FVC and mean PEF from baseline after inhaled beclomethasone and the change seen in the four dimensions of the quality of life questionnaire, in the oxygen cost diagram, and diary card breathlessness scores was poor (table 7.4.).

Both responders and non responders to inhaled beclomethasone, classified on the basis of changes in FEV1, FVC and mean PEF, showed significant improvements in quality of life questionnaire dyspnea scores, but only responders showed an effect of active treatment in the other three components of the questionnaire. The diary card breathlessness scores improved in physiological responders, but there was no significant difference from baseline values in the non responders. Oxygen cost diagram scores were improved after both placebo and inhaled beclomethasone in non responders, but there was no significant difference from placebo after active therapy. In responders no significant change after either placebo or inhaled beclomethasone was detected (table 7.5.).

Table 7.4. Spearman rank correlation coefficients for the association between the change from baseline after inhaled beclomethasone in subjective measures and in FEV1, FVC, and mean PEF.

Change in	FEV1	FVC	mean PEF
Dyspnea	0.17	0.16	0.26*
Fatigue	0.23*	0.20	0.10
Emotional function	0.17	0.14	0.19
Mastery	0.29*	0.24*	0.17
SOB	-0.11	-0.11	-0.25*
O2cost	-0.01	0.06	0.03

Dyspnea - quality of life questionnaire dyspnea score  
 SOB - diary card breathlessness score  
 O2cost - oxygen cost diagram score

\*  $p < 0.05$ .

Table 7.5. The mean (SEM) scores for the four components of the quality of life questionnaire, the oxygen cost diagram (O2cost), and diary card breathlessness score (SOB). At baseline, after placebo and inhaled beclomethasone, in responders and non responders defined on the basis of lung function changes, (see text for statistical significance of differences).

	Baseline	Placebo	BDP
<i>Dyspnea</i>			
Responders	17.6 (0.9)	19.2 (1.2)	21.2 (1.4)
Non responders	18.0 (0.6)	19.2 (0.7)	20.7 (0.8)
<i>Fatigue</i>			
Responders	17.8 (0.9)	17.2 (0.8)	18.8 (0.9)
Non responders	17.4 (0.7)	17.4 (0.6)	17.8 (0.7)
<i>Emotional function</i>			
Responders	32.6 (1.7)	33.4 (1.6)	35.6 (1.7)
Non responders	33.4 (1.0)	34.5 (1.1)	34.4 (1.1)
<i>Mastery</i>			
Responders	18.9 (1.1)	19.8 (1.1)	20.8 (1.1)
Non responders	20.4 (0.7)	20.8 (0.7)	21.2 (0.7)
<i>O2 cost</i>			
Responders	114 (6.5)	119 (7.3)	118 (7.2)
Non responders	122 (4.8)	129 (5.2)	131 (4.7)
<i>SOB</i>			
Responders	3.1 (0.2)	3.2 (0.2)	2.7 (0.2)
Non responders	2.9 (0.2)	3.0 (0.2)	2.77(0.2)

Ninety three of the 98 patients completing the second treatment phase had complete data for classification into *subjective* responders or non responders. Forty one patients showed an increase in the physical function dimension of the quality of life questionnaire of greater 4 after inhaled beclomethasone, and were classed as subjective responders. Of these 19 were in the 750mcg b.d. group, and 22 in the 1500mcg b.d. The difference between the subjective response rate to the two doses was not significant (chi-squared=0.28,DF=1,ns).

Twenty three patients showed a subjective response after placebo. The difference between the subjective response to placebo

and both doses of inhaled beclomethasone was statistically significant (table 7.6.).

When the change in FEV1, FVC, and mean PEF after inhaled beclomethasone from baseline were compared in the two subjective response groups, no significant differences were seen. However in every objective physiological measure the subjective responders did show a larger mean improvement (figure 7.2.).

The change in the physical function score ( the sum of the dyspnea and fatigue elements ) was correlated poorly with the change in each of the objective measures of lung function,(Pearson correlation coefficients were FEV1 0.16, FVC 0.14, mean PEF 0.19).

Table 7.6. Subjective response to inhaled beclomethasone and placebo in individual patients.

Placebo	Beclomethasone	
	Responder	Non responder
Responder	19	4
Non responder	22	48

McNemar test  $p < 0.001$

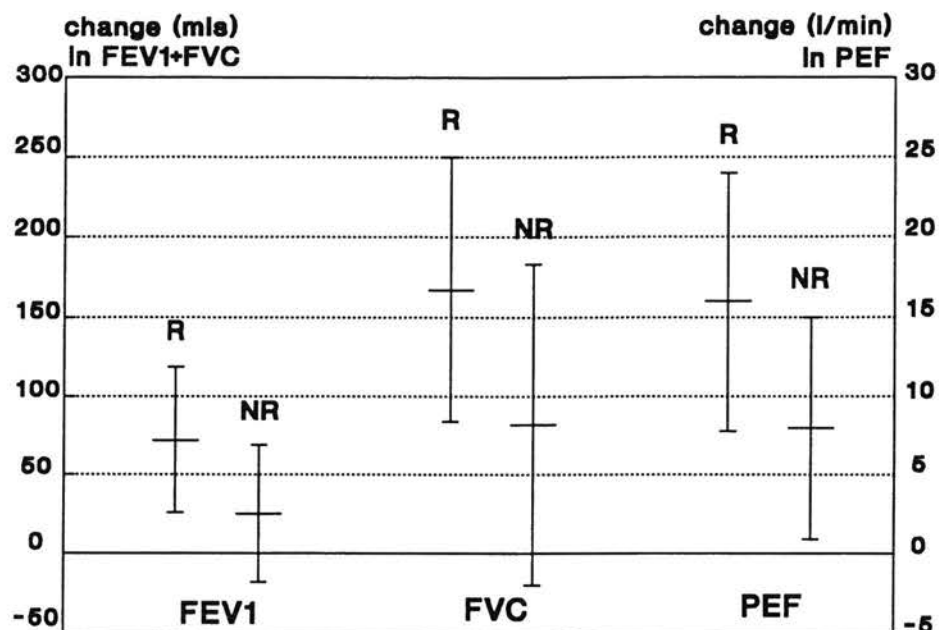


Figure 7.2. The change from baseline after treatment with inhaled beclomethasone in FEV1, FVC and mean PEF in *subjective* responders(R) and non responders(NR) to treatment classified according to change in quality of life questionnaire scores.(Error bars show mean and 95% CI for the difference).

### **7.2.3. The effect of oral prednisolone.**

The change in the dyspnea, fatigue and emotional function elements of the quality of life questionnaire, from that recorded at the end of the second treatment phase, was not significantly different in the patients receiving oral prednisolone during the third treatment phase and those patients continuing on inhaled beclomethasone alone (table 7.7). The latter group showed larger mean changes in the three area of the quality of life questionnaire, but the mastery dimension was the only component in which the differences between the dose groups were statistically significant.

The changes in the oxygen cost diagram and diary card breathlessness scores were also similar between the two third phase treatment groups.

Of the patients completing the final treatment phase 89 had data to allow classification of subjective response. A subjective response was seen in 14/30 of the patients continuing on inhaled beclomethasone alone, and in 31/59 of the patients who received both oral prednisolone and inhaled beclomethasone during the third treatment phase. The difference was not significant (chi squared=0.27, DF=1, ns).

Table 7.7. The changes in each of the subjective measures over the third treatment phase. BDP - inhaled beclomethasone alone, BDP+PRED - inhaled beclomethasone plus oral prednisolone 40mg per day.

	Treatment group	
	BDP (n=32)	BDP+PRED (n=61)
Dyspnea	1.7 (0.9 to 2.9)	0.7 (-0.1 to 1.5)
Fatigue	1.1 (0.05 to 2.2)	0.5 (-0.4 to 1.4)
Emotional Function	1.7 (-0.08 to 3.5)	0.4 (-0.9 to 1.6)
Mastery	1.1 (0.4 to 1.7)	-0.1 * (-0.7 to 0.5)
O2cost	4.9 (-5.1 to 14.9)	2.3 (-3.8 to 8.5)
SOB	-0.1 (-0.4 to 0.2)	0.1 (-0.05 to 0.3)

\*  $p < 0.05$

Dyspnea - quality of life questionnaire dyspnea score

SOB - diary card breathlessness score

O2cost - oxygen cost diagram score



### 7.3. DISCUSSION.

This is the first study which has looked at the effects of inhaled and oral corticosteroids on physiological function in chronic airflow obstruction and has also assessed subjective response by using a formal 'quality of life' instrument. In past studies therapeutic benefit has usually been assessed in terms of physiological change, with some studies also assessing change in the subjective sensation of breathlessness, and global assessments of general well being(83,84,90,92).

The relationship between decreased lung function and impaired well being in day to day functioning is complex and incompletely understood. Previous studies have shown a poor correlation between measures of airflow obstruction and simple measures of disability, such as the MRC breathlessness score, oxygen cost diagram and Mahler dyspnea index (83,167,188). Individual variability in the perception of breathlessness seems to be more important than differences in the degree of airflow obstruction in determining disability. It therefore seems appropriate to include in the assessment of effects of therapy a measure of the change in the patients life and perceived well being, in addition to symptom indices. The use of such a 'quality of life' instrument gave additional information in a previous study looking at the effects of oral theophylline and inhaled salbutamol in patients with chronic airflow obstruction(187).

The results of the measures of dyspnea used show an improvement in the dyspnea index of the quality of life questionnaire and the diary card breathlessness scores after inhaled beclomethasone, but a marked placebo effect in the results of the oxygen cost diagram. As with objective measures of lung function, the effect of the two doses of inhaled beclomethasone used was broadly similar. The lack of a dose effect is probably a reflection of the mode of delivery of the drug, and the dose response characteristics of inhaled beclomethasone as outlined in the previous chapter.

The remaining components of the quality of life questionnaire

showed variable placebo effects but the mastery element, the feeling of control over the disease process, was the only component showing a significant effect of treatment with inhaled beclomethasone. The addition of oral prednisolone over the final treatment phase caused no further significant change in any of the indices of dyspnoea, or the fatigue and emotional function components of the quality of life questionnaire, but patients continuing on inhaled beclomethasone alone showed an increase in the mastery score, not seen in patients receiving both oral prednisolone and inhaled beclomethasone.

Our definition of a subjective response to treatment was based upon Guyatt's unsupported comments that an improvement of 4 or more in the physical function element of the questionnaire represents a clinically important difference. Using his definition of subjective response, inhaled beclomethasone produced more subjective responders than placebo therapy and no differences in the subjective response rate to the two doses of beclomethasone was seen. After the addition of oral prednisolone to the regime of 2/3 of the patients during the final treatment phase, the subjective response rate was similar between those continuing on inhaled beclomethasone alone and those receiving oral prednisolone and inhaled beclomethasone.

The mean changes seen in all the subjective measures used were small in absolute terms. The mean improvement in the dyspnea and mastery dimensions of the quality of life questionnaire were similar however to that seen with treatment with simple bronchodilators(187).

Studies of corticosteroids which have formally assessed change in subjective measures have shown variable, and usually low order correlations between changes in the subjective measures and changes in lung function variables. This divergence emphasises the indirect link between measures of airflow obstruction and disability. Williams & McGavin found a reasonably strong correlation between changes in FVC and a visual analogue assessment of what appears to be global well being(75). However in Lam et al's study the change in FVC showed the weakest correlation with the change in dyspnoea

score, with larger significant correlations seen between change in FEV1 and change in peak flow(90). The strongest correlation was seen between the change in FEV1 and change in dyspnea score, but only 40% of the variance in the dyspnoea score was explained by the change in FEV1. O'Reilly et al used a subjective assessment of walking ability, the oxygen cost diagram(167), and the Borg rating of perceived exertion to assess subjective response(83). In their study the only significant correlation seen between change in FEV1 or FVC and subjective measures was that between change in FEV1 and the improvement in the oxygen cost diagram. Other investigators in a slightly larger group of patients found the change in a breathlessness score and the oxygen cost diagram correlated significantly but weakly with the change in FVC and the change in the breathlessness score alone with the change in FEV1(92). An assessment of well being using a visual analogue scale correlated poorly with changes in objective measures. However all these studies contained relatively small numbers of patients, and used crude unrefined instruments to measure subjective aspects of disease.

In the larger NOTT study which looked at the relationship between a general quality of life instrument, the Sickness Impact Profile (SIP)(189), and lung function in over 200 patients with COPD the correlations between physiological measures of disease severity and the results of the quality of life instrument were also of a low order(190). A further study designed to specifically evaluate the usefulness of the same quality of life instrument in patients with chronic airflow obstruction looked at 141 patients with a wider range of disability(191). In this study the correlation between spirometric measures, peak flow and the quality of life scores were again low with the largest correlation being seen between FVC and quality of life. Even with this spirometric measure, less than 20% of the variance of the quality of life score was explained by the FVC. The largest correlation in this study was seen between 6 minute walking distance and quality of life score, suggesting that the same attitudes and expectations which predict walking speed and distance appear to influence patients perception of their quality of life.

The authors showed that this general quality of life

questionnaire (SIP) appeared to be a relatively insensitive tool in patients with mild airflow obstruction. Patients with breathlessness scores indicating moderate disability showed no difference in SIP scores, but as disability scores worsened so the difference in SIP scores became more marked. In addition 20% of all the items in the SIP questionnaire were left unanswered by patients with chronic airflow obstruction as they were irrelevant to their daily life. The implication is that a disease specific quality of life questionnaire may provide more information than a general measure.

The quality of life instrument used in the present study was developed in Canada in a population of patients with chronic airflow obstruction and is disease specific unlike the quality of life instrument used in the studies quoted above(166). As such the noise in any treatment effect should be less, and hence the instrument should be more sensitive than the general quality of life measures. Guyatt has shown that the instrument is responsive to change in disease state and that it appears to be a valid measure. The coefficient of variation for repeated administration at 2 week intervals is 6% for the dyspnoea dimension, 9% for both fatigue and emotional function and 12% for mastery. This compares favorably for the coefficient of variation for the measurement of FEV1 (15%), FVC (11%) and single breath carbon monoxide gas transfer (15%) in patients with chronic airflow obstruction(192).

That this quality of life questionnaire measures something in addition to lung function changes is clear from the poor correlation seen between changes in the elements of the quality of life questionnaire and changes in FEV1, FVC and mean peak flow. Although Guyatt claims in his hands to see moderate correlations between changes in the quality of life questionnaire and changes in the lung function, the actual correlations have not been fully published and hence it is difficult to compare the results in this study with his own. The strongest correlations between the quality of life elements and objective measures of lung function in the present study were seen between FEV1 and FVC, and mastery, and between the change in mean peak flow and the change in the dyspnoea dimension score. In addition, the change in mean peak flow showed a

moderate correlation with the diary card breathlessness score changes but no correlation at all with the changes in the oxygen cost diagram. It is my impression that patients have difficulty understanding the instructions for completing the oxygen cost diagram, often requiring further explanation and assistance in completing it and this may be why this particular instrument appears to be relatively insensitive.

The improvement seen in the quality of life elements, although statistically significant were small. Compared to the improvement seen by Guyatt et al after a rehabilitation program, the effect of inhaled beclomethasone appears to be much smaller(166). However they are only slightly less than the changes seen after oral and inhaled bronchodilator treatment(187,193). It is difficult to truly compare the results of this present study with those of Guyatt et al as information on the age, sex and lung function of the patients studied by Guyatt et al is not available. It may be that my study investigated patients with more severe disease, who had, therefore, a smaller potential for improvement with treatment. It also seems likely that such features as reversibility of airflow obstruction and possibly smoking habit would also affect the response in terms of quality of life to various treatments. In addition many of the patients recruited to my trial had other coexistent medical problems (eg; angina, osteoarthritis, depression) which may have a bearing on their responses to the quality of life questionnaire.

It is also likely that improvement in quality of life will lag behind any improvement in physiological measures. Patients will require time to adapt to the improved physiological function, and to regain confidence. Many of the factors relating to impaired quality of life will only be indirectly related to airflow obstruction, eg exercise limitation due to breathlessness causing disuse atrophy of limb muscles. Another possible explanation for the small improvements seen in the present study is that in addition to being disease specific, the quality of life questionnaire of Guyatt et al may also have cultural specificity. It is possible that patients in the UK perceive functional disability in a different manner to those in North America.



Although change in the objective physiological measures used did not correlate well with changes in the quality of life or breathlessness assessments, there was a difference in the effect of treatment on subjective measures in patients classified as physiological responders to treatment compared to those who did not respond to treatment in term of change in FEV1, FVC or mean peak flow. On first sight, this is surprising, but one explanation may be that physiological response was based upon the change on three objective variables, hence a simple correlation with change in single variables may well be lacking. The fact that a subjective response to treatment was seen in all dimensions of the quality of life questionnaire in physiological responders seems to justify the somewhat arbitrary traditional definition of physiological response used. The classification adopted does appear to differentiate between patients showing an improvement in subjective measures, and those not. Only the oxygen cost diagram, with the problems attached to its completion noted above, failed to show any difference between physiological responders and non-responders.

Conversely, defining response on the basis of subjective measures alone, using Guyatt's cut-off, of an improvement of 4 in the physical function element of the questionnaire, did not produce two distinct patient populations in terms of treatment effect on physiological variables. Although subjective responders did show higher mean changes after treatment with inhaled beclomethasone in FEV1, FVC and mean PEF, there was no statistically significant difference between the two subjective response groups. That aside, only the subjective responders showed a change in each of the three objective parameters which is significantly different from zero after treatment. Guyatt et al's justification for a cut off of 4 is not clear, but re-analysis of the data in this study shows similar results, whether the cut off is raised to 5 or 6.

It is perhaps not surprising that the addition of oral prednisolone caused no significant improvement in the subjective measures investigated. As no significant improvements in the objective measures were seen with oral prednisolone and one may presume that the other factors affecting response to subjective

measures were constant, it is likely that no change would be detected in the subjective measures. The mastery dimension of the quality of life questionnaire did show differences between the final treatment groups, but the effect was small. Studies looking specifically at prednisolone induced mood changes in this group of patient, have come to conflicting conclusions. Mitchell et al failed to distinguish between a euphoriant action of prednisolone and a placebo effect(194), although Swinburn et al detected a mild inappropriate well being after treatment with oral prednisolone(77). The results seen in the present study would also suggest that any euphoriant effect of prednisolone is mild.



## **8. THE EFFECT ON BRONCHIAL RESPONSIVENESS TO INHALED HISTAMINE.**

### **8.1. ANALYSIS.**

Comparison of the effect of placebo and inhaled beclomethasone dipropionate on bronchial responsiveness to inhaled histamine was assessed by a repeated measures analysis of variance with dose of inhaled drug entered as a factor. A logarithmic transformation of PD20 was used in the analysis.

The additional effect of treatment with oral prednisolone was determined by comparing the change in bronchial responsiveness to inhaled histamine from that recorded after the inhaled beclomethasone treatment phase to that at the end of the final treatment phase, in patients receiving oral prednisolone and those continuing on inhaled beclomethasone alone. For this analysis bronchial responsiveness as measured by the method of Yan(163), PD20, at the end of each treatment phase was used.

The correlation between the degree of airflow obstruction and bronchial responsiveness to inhaled histamine, and between the three baseline measures of bronchial responsiveness was determined by estimation of the Pearson correlation coefficients. Repeatability of PD20 measurements was expressed in terms of the 95% range for a single measurement.

## 8.2. RESULTS.

### 8.2.1. Distribution of bronchial hyperresponsiveness to inhaled histamine, correlation with baseline variables, and repeatability of the measure.

Seventy four patients with an FEV1 greater than 0.75 litres had bronchial responsiveness to inhaled histamine measured during the baseline period. After placebo treatment and the inhaled beclomethasone treatment phase PD20 was measured in 65 of these patients, and after the final treatment in 60 subjects. In three of the 74 patients the fall in FEV1 after the final dose of histamine (7.8umol) was less than 20%. Extrapolation allowed a value to be determined in two cases, in the third a value for PD20 of 16 micromol was used in the analysis.

The majority of patients showed a moderate degree of bronchial hyperresponsiveness to inhaled histamine, with only 19 patients having a PD20 value of less than 0.24umol histamine. The median PD20 value was 0.45umol histamine, and the geometric mean PD20 0.52umol histamine. The distribution of PD20 values is shown in figure 8.1.

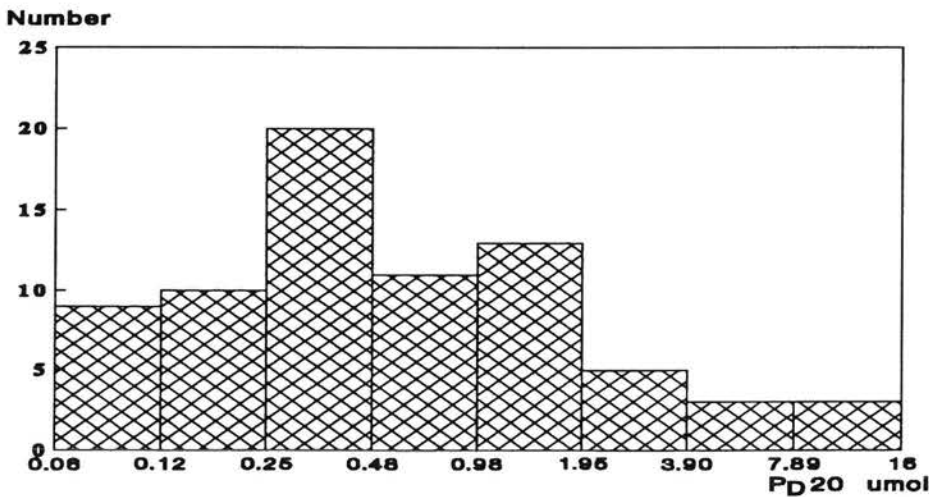


Figure 8.1. The distribution of PD20 values in the 74 patients at baseline.

Moderate correlations between the severity of bronchial hyperresponsiveness to inhaled histamine and the severity of airflow obstruction measured as FEV1/FVC ratio, FEV1 alone or PEF were seen (table 8.1.). Lower order correlations were seen between indices of reversibility and PD20, but no significant correlation was seen between PD20 and diurnal variation in PEF. The relationship between PD20 and FEV1/FVC is shown in figure 8.2..

The correlation between the logarithm of bronchial responsiveness to inhaled histamine measured by the two different methods was, perhaps not surprisingly, high ( $r=0.81$ ). The correlation between bronchial hyperresponsiveness to inhaled histamine, measured by the Yan method, and responsiveness to ultrasonically nebulised distilled water was much less. In 38 patients in which the result of the test of bronchial responsiveness to ultrasonically nebulised distilled water was not censored the Pearson correlation coefficient between the log transformed values was 0.34.

Table 8.1. Pearson correlation coefficients between various lung function measures and log PD20.

FEV1 litres	0.43 ***
% predicted	0.39 **
FEV1/FVC ratio	0.42 ***
mean PEF l/min	0.45 ***
% predicted	0.27 *
Diurnal variation in PEF	
as % mean	-0.11
as % predicted	0.02
FEV1 reversibility to 200mcg salbutamol	
as absolute change (ml)	-0.21
as % of predicted FEV1	-0.23

\*\*\*  $p < 0.001$ , \*\*  $p < 0.01$ , \*  $p < 0.05$ .

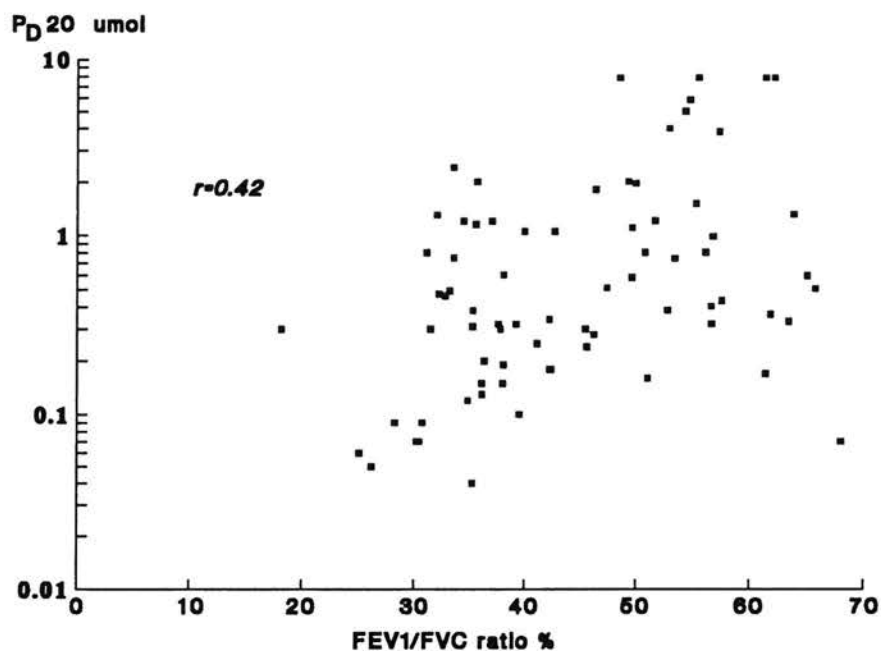


Figure 8.2. Scatterplot of the relationship between the degree of airflow obstruction, as FEV1/FVC ratio, and the severity of bronchial hyperresponsiveness, PD20.

In the 66 patients who had PD20 measured at baseline and after placebo treatment, the standard deviation for the difference between repeat PD20 measurements was 0.97 log<sub>10</sub> units, giving a 95% range for a single estimation of PD20 of 1.99 doubling concentrations of histamine. The values for individual patients are shown in figure 8.3.

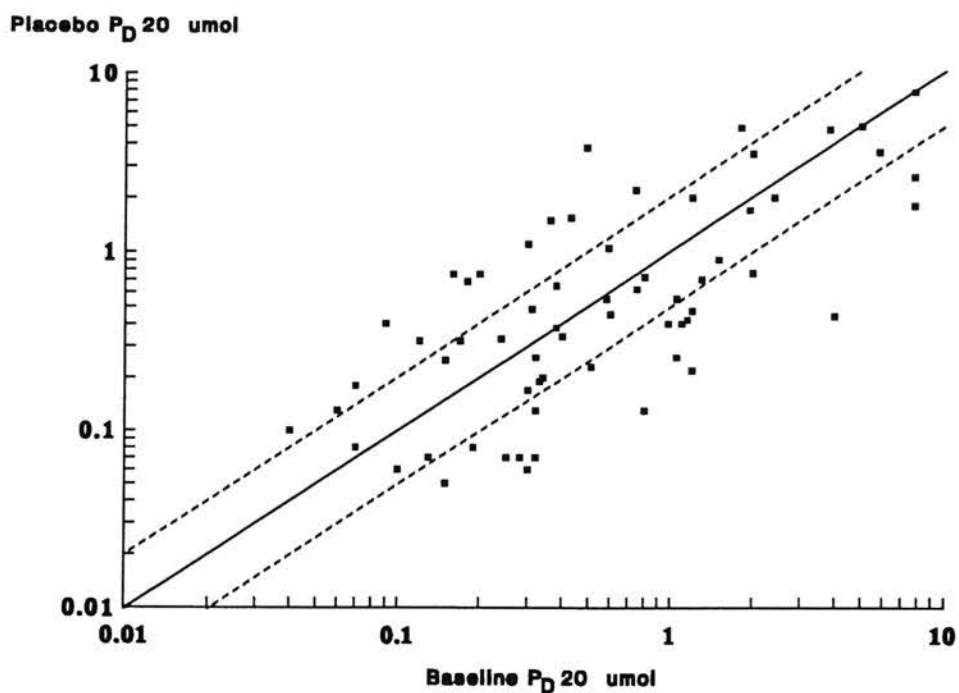


Figure 8.3. Relation between PD20 values from tests at baseline and after placebo treatment. The solid line is the line of identity and the dotted lines indicates one doubling dose from the line of identity.

### 8.2.2. The effect of inhaled beclomethasone.

After treatment with placebo or inhaled beclomethasone there was no significant change in bronchial responsiveness to inhaled histamine from that measured during the baseline period. Table 8.2. shows the geometric mean PD20 value for the two inhaled beclomethasone dose groups. The lack of any improvement in PD20 was despite a small improvement in FEV1 with treatment in both dose groups. In patients receiving 750mcg b.d. inhaled BDP the FEV1 improved from a mean (95% CI) at baseline of 1.29 (1.19 to 1.39) litres, to 1.34 (1.24 to 1.44) after inhaled beclomethasone. After placebo treatment the FEV1 was not significantly different from baseline (placebo FEV1, mean 1.27 (1.17 to 1.37)). In those receiving the higher dose of inhaled beclomethasone the FEV1 increased from a baseline value of 1.27 (1.15 to 1.38) litres to 1.32 (1.19 to 1.45) after active treatment, the mean (95% CI) FEV1 after placebo were not different from baseline (1.27 (1.14 to 1.41) litres).

Figure 8.4. shows the change in PD20 values in individual patients after placebo and inhaled beclomethasone, with the change expressed as doubling doses of histamine. From this it is clear that very few patients had changes in PD20 after active treatment greater than the 95% limits for repeatability of the measurement.

To exclude an effect of measurement error on PD20 in patients with the lowest FEV1 values, ie FEV1 0.75 to 1.2, where a 20% fall in FEV1 approximates the short term limits of repeatability of measurement of FEV1(94), the analysis was repeated on patients with an FEV1 of greater than 1.2 litres. In this subgroup there was no detectable effect of inhaled beclomethasone on bronchial responsiveness to inhaled histamine. The geometric mean PD20 values at baseline (for both dose groups combined) were 0.84umol, after placebo 0.28 umol, and after inhaled beclomethasone 1.08umol.

Table 8.2. Geometric mean PD20 values at baseline, after placebo and inhaled beclomethasone for both dose groups.

750mcg b.d. group.	
Baseline	0.56 umol
Placebo	0.49 umol
BDP	0.61 umol
1500mcg b.d. group.	
Baseline	0.65 umol
Placebo	0.51 umol
BDP	0.58 umol
Treatment effect F-ratio 1.5,	ns
Interaction F-ratio 0.45,	ns

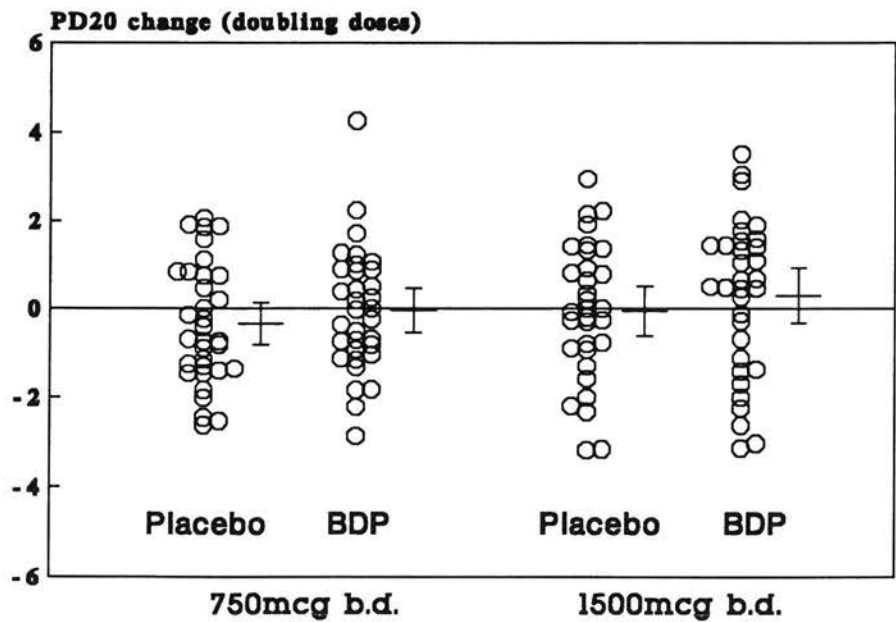


Figure 8.4. The change from baseline in individual PD20 values after placebo and inhaled beclomethasone. Error bars show mean and 95 % confidence limits for mean of the difference. The change in PD20 values is expressed in doubling doses (log2 units) of histamine.



It might be argued that patients with little or normal bronchial responsiveness to inhaled histamine would be expected to show small or no treatment effects. Hence an analysis was performed after classifying patients into severe and moderate bronchial hyperresponsiveness. Patients with a PD<sub>20</sub> of 1 μmol or less at baseline were classed as severe bronchial hyperresponsiveness. In this group a small but statistically significant improvement in bronchial responsiveness was seen after treatment with inhaled beclomethasone. The geometric mean PD<sub>20</sub> improved from 0.26 μmol at baseline, and 0.28 μmol after placebo to 0.40 after inhaled beclomethasone (treatment effect F-ratio=3.88,  $p < 0.03$ ). However in those with less severe bronchial hyperresponsiveness (PD<sub>20</sub> greater or equal to 1 μmol) PD<sub>20</sub> values fell significantly after placebo (geometric mean (μmol); baseline 2.41, placebo 1.39, BDP 1.40 Treatment effect F-ratio = 6.9,  $p < 0.01$ ), suggesting the effect seen in the group with severe bronchial hyperresponsiveness may simply represent regression to the mean.

The effect of treatment on bronchial responsiveness to inhaled histamine in patients who had shown a response to inhaled BDP was examined by comparing the change in PD<sub>20</sub>, expressed in doubling concentrations, from the end of the placebo period to that measured after inhaled beclomethasone. In the 18 patients classed as responsive to BDP the PD<sub>20</sub> improved by a mean (95% CI) 0.37 (-0.66 to 1.4) doubling concentrations, in the non responders the improvement was similar, mean 0.31 (-0.08 to 0.71).

### 8.2.3. The effect of oral prednisolone.

Of the 60 patients who had PD20 measured after the final treatment phase, 38 received oral prednisolone in addition to inhaled beclomethasone at the dose taken during the second treatment period. The remaining 22 continued on inhaled beclomethasone alone, 11 in each beclomethasone dose group.

After six weeks treatment with inhaled BDP alone there was no detectable effect of treatment on PD20. The geometric mean PD20 values in the two dose groups are shown in table 8.3..

Oral prednisolone 40mg per day for three weeks also had no significant effect on bronchial responsiveness to inhaled histamine. In the 38 patients who received both oral prednisolone and inhaled beclomethasone the geometric mean PD20 value fell from 0.62umol after inhaled beclomethasone alone, to 0.59umol after oral prednisolone ( $t=0.284$ ,ns).

In the 22 patients receiving inhaled beclomethasone alone the PD20 value fell on average by 0.41 doubling concentrations of histamine, in the patients receiving both oral prednisolone and inhaled beclomethasone the mean change was an improvement of 0.06 doubling concentrations. The changes in individual patients are shown in figure 8.5..

The effect of oral prednisolone was similar in patients with a PD20 value less than 1 umol, and in patients in whom the FEV1 was greater than 1.2 litres at baseline.

Table 8.3. The geometric mean PD20 values at baseline, after placebo and after three and six weeks treatment with inhaled beclomethasone for both dose groups.

750mcg b.d. group.	
Baseline	0.74 umol
Placebo	0.90 umol
3 weeks BDP	0.68 umol
6 weeks BDP	0.70 umol
1500mcg b.d. group.	
Baseline	0.29 umol
Placebo	0.27 umol
3 weeks BDP	0.51 umol
6 weeks BDP	0.28 umol
Treatment effect F-ratio 0.58,	ns
Interaction F-ratio 1.4,	ns

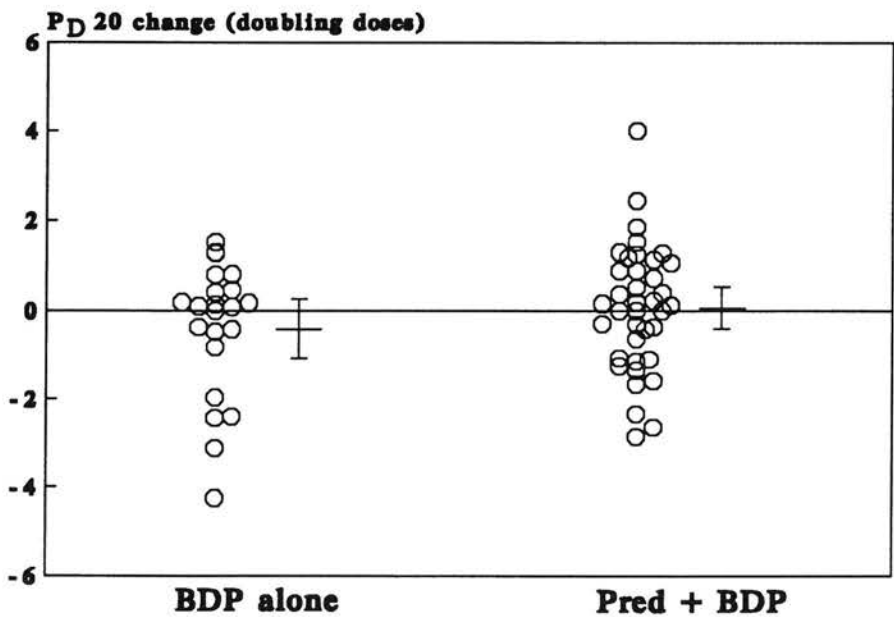


Figure 8.5. The effect of treatment with oral prednisolone on PD20 values. The change in doubling doses of histamine from the value recorded after BDP alone, and after the final treatment phase is shown for individual patients. The error bars show the mean change and 95% confidence limits for the mean.

### 8.3. DISCUSSION.

The results show no significant effect of inhaled beclomethasone or oral prednisolone on bronchial hyperresponsiveness to inhaled histamine in these patients with chronic airflow obstruction. The lack of any effect is despite a small increase in FEV1 in the patients, which because of the correlation between FEV1 and PD20 would tend to decrease bronchial hyperresponsiveness(124). In a post hoc sub-group analysis a statistically significant but small effect was seen in patients with more severe bronchial hyperresponsiveness. However this change may be explained by regression to the mean, and the increase in mean PD20 values was considerably less than one doubling concentration of histamine.

The measurement of bronchial responsiveness to inhaled histamine is usually restricted to patients with less severe chronic airflow obstruction, partly because of theoretical safety concerns, and also because of difficulty in interpreting the results of tests. In patients with an FEV1 less than one litre a 20% fall in FEV1 induced by histamine will produce an absolute fall which is just greater than the short term variability of the measurement, so that the validity of the measurement of PD20 may be open to question. However the repeatability of the measurement in all the patients studied for this thesis is similar to that seen in asthmatics(195), and in epidemiological studies of normal subjects, where concerns about the validity of a 20% fall in FEV1 do not occur. It would appear therefore that the measurement of PD20 in these patients with severe chronic airflow obstruction is valid. In addition the reanalysis of the data excluding patients with an FEV1 of less than 1.2 litres did not significantly affect the conclusions of the effect of treatment on bronchial hyperresponsiveness.

A number of studies have shown an improvement in bronchial hyperresponsiveness after treatment with inhaled corticosteroids in patients with asthma(113,115,196). However none of the four published studies investigating the effect of corticosteroids on bronchial hyperresponsiveness in patients with chronic bronchitis and or chronic airflow obstruction has reached positive

conclusions(132-134,197).

There are a number of possible explanations for the different effect of inhaled corticosteroids in asthma and chronic airflow obstruction. Recent histological studies have suggested that in asthma the cellular component of bronchial wall inflammation is primarily eosinophilic(32,33), whereas in chronic airflow obstruction the inflammation in the bronchial wall appears to be mainly composed of neutrophils(139,148). It is possible that the lack of an effect of corticosteroids on bronchial hyperresponsiveness in chronic airflow obstruction is explained by a reduced sensitivity of neutrophilic inflammation to suppression with corticosteroids.

In this study treatment was given for 2 sequential three week periods. It is possible a longer period of treatment would produce changes in bronchial responsiveness to inhaled histamine. In asthma the effect of eight weeks treatment with inhaled corticosteroids is far greater than the effect seen at 2-3 weeks(113). In Postma et al's retrospective study the beneficial effects of oral corticosteroids on decline in FEV1 were not seen until at least 6 months after treatment was instituted, suggesting prolonged treatment with corticosteroids may be required to observe a beneficial effect(57). However one may have expected a trend towards improvement in bronchial hyperresponsiveness to be apparent after six weeks, and this is not evident either in my data, nor in a study where the effect on PD20 of eight weeks treatment with inhaled budesonide was assessed(134). Other workers did not detect any effect of treatment with inhaled budesonide at a dose of 600mcg twice daily on bronchial hyperresponsiveness in an open study of smokers with a documented accelerated decline in FEV1(133). A prospective study investigating the effect of inhaled beclomethasone on bronchial hyperresponsiveness over two years is currently underway in our centre.

An alternative explanation for the lack of an effect of treatment on bronchial hyperresponsiveness in chronic airflow obstruction may be that the primary determinant of bronchial hyperresponsiveness in chronic airflow obstruction is geometric

rather than inflammatory. In asthmatic patients the degree of bronchial hyperresponsiveness and airway obstruction are largely independent, that is many patients show normal FEV1 values but severe bronchial hyperresponsiveness. In patients with chronic airflow obstruction the degree of bronchial responsiveness correlates strongly with the degree of airflow obstruction. Yan et al found a correlation between FEV1/FVC ratio and PD20 of  $r=0.7(124)$ . The correlation was less in my study, but still highly statistically significant, suggesting a close link between bronchial hyperresponsiveness and airflow obstruction.

A number of other observations suggest bronchial wall inflammation is not the major cause of bronchial hyperresponsiveness in the patients studied. The two doses of inhaled beclomethasone used would be expected to have significant anti-inflammatory effects on the bronchial mucosa, but despite this no significant change in PD20 was seen. In smokers bronchodilators alone, with no anti-inflammatory properties, improve bronchial hyperresponsiveness over the short term, probably as a result of the bronchodilation induced(133). The lack of any major effect of corticosteroids on PD20 in patients classed as responders to treatment in my study would also support the argument that geometric factors are the primary determinant of bronchial hyperresponsiveness in chronic airflow obstruction. It also implies that the underlying pathology in the bronchial wall is not asthmatic, ie; eosinophilic, and supports the contention that the patients studied are not simply 'missed asthmatic'.

## ***9. THE EFFECT ON GLOBAL RESPIRATORY MUSCLE STRENGTH AS MEASURED BY MAXIMAL STATIC MOUTH PRESSURES.***

### **9.1. ANALYSIS.**

In order to eliminate any possible learning effect in the measurement of maximal static mouth pressures(198), the baseline values were taken as those recorded on the latter of the two baseline days when mouth pressures were measured. The change in maximal inspiratory mouth pressure, P<sub>imax</sub>, and maximal expiratory mouth pressure, P<sub>emax</sub>, after inhaled beclomethasone was assessed by a repeated measures analysis of variance, with dose of drug entered as a factor. Where significant effects were detected a Fisher's LSD test was used to determine which comparisons were significant. For analysis of the data after the final phase of active treatment, when two thirds of the patients received oral prednisolone in addition to inhaled beclomethasone, the change in each variable from the previous phase was calculated. The change was compared between patients receiving or not receiving prednisolone by an unpaired Student *t* test, combining the inhaled beclomethasone dose groups.

Pearson correlation coefficients between baseline physiological variables and maximal static mouth pressures were calculated to assess associations.



## **9.2. RESULTS.**

### **9.2.1. Data collection, and baseline correlations.**

Measurement of both maximal inspiratory mouth pressure (Pimax), and maximal expiratory mouth pressure (Pemax) was performed in 103 patients at baseline (2 patients were unable to perform the test adequately). After placebo therapy values for both variables were available in 97 patients, and after inhaled beclomethasone in 96 patients for Pimax, and 95 for Pemax. After the final treatment phase measurements were available in 90 patients for Pimax, and 89 patients for Pemax.

The association between Pimax and Pemax, and various baseline lung function measurements and body mass index is shown in table 9.1.. Correlations are significantly lower when allowance is made for age and height by expressing lung function variables as a percentage of the predicted value.

Evidence for a small learning effect in the measurement of maximal static mouth pressures was obtained by comparing the values obtained on the first baseline occasion with those from the second measurement. Pimax improved by a mean (95% CI) of 3.2 (5.3 to 1.1) cm H<sub>2</sub>O, and Pemax by a mean of 5.3 (8.4 to 2.1) cm H<sub>2</sub>O.

Table 9.1. Pearson correlation coefficients between Pimax and Pemax, and various measures of lung function and body mass index.

	Pimax	Pemax
FEV1 (litres)	0.35 ***	0.24 *
as % predicted	0.18	0.01
FVC (litres)	0.44 ***	0.39 ***
as % predicted	0.21 *	0.02
FEV1/FVC	0.06	-0.05
TLC	0.35 ***	0.38 ***
as % predicted	0.06	-0.04
RV/TLC	-0.24 *	-0.16
mean PEF	0.44 ***	0.46 ***
as % predicted	0.32 ***	0.33 ***
BMI (wt/ht <sup>2</sup> )	0.12	0.33 ***

RV- residual volume (litres)

TLC- total lung capacity (litres)

BMI- body mass index = weight (kg)/ height (kg) squared.

\*\*\* p < 0.001, \* p < 0.05.

### 9.2.2. The effect of inhaled beclomethasone.

#### a. Maximal inspiratory mouth pressure.

In the 96 patients in whom Pimax was measured at baseline, and after placebo and inhaled beclomethasone there was a significant, though small increase after active therapy. There was no significant difference between the two dose groups detected (table 9.2.). The change from baseline after placebo and inhaled beclomethasone for the two dose groups is shown graphically in figure 9.1..

#### b. Maximal expiratory mouth pressure.

For maximal expiratory mouth pressure no significant effect of treatment with inhaled BDP was noted (table 9.2.).

Table 9.2. The mean (SEM) for maximal inspiratory mouth pressure, and maximal expiratory mouth pressure at baseline, and after placebo and inhaled beclomethasone.

BDP dose	Baseline	Placebo	BDP
<i>Pimax</i>			
750mcg b.d.	56.6 (3.3)	57.4 (3.3)	60.0 (3.6)
1500mcg b.d.	58.0 (2.7)	57.3 (2.6)	61.5 (3.1)
Treatment effect F-ratio=8.7, DF=2, $p < 0.0003$ .			
Dose effect F-ratio=0.45, DF=2, ns.			
<i>Pemax</i>			
750mcg b.d.	128 (6.2)	127 (6.0)	130 (6.2)
1500mcg b.d.	133 (5.4)	134 (2.6)	135 (5.9)
Treatment effect F-ratio=0.92, DF=2, ns.			
Dose effect F-ratio=0.11, DF=2, ns.			

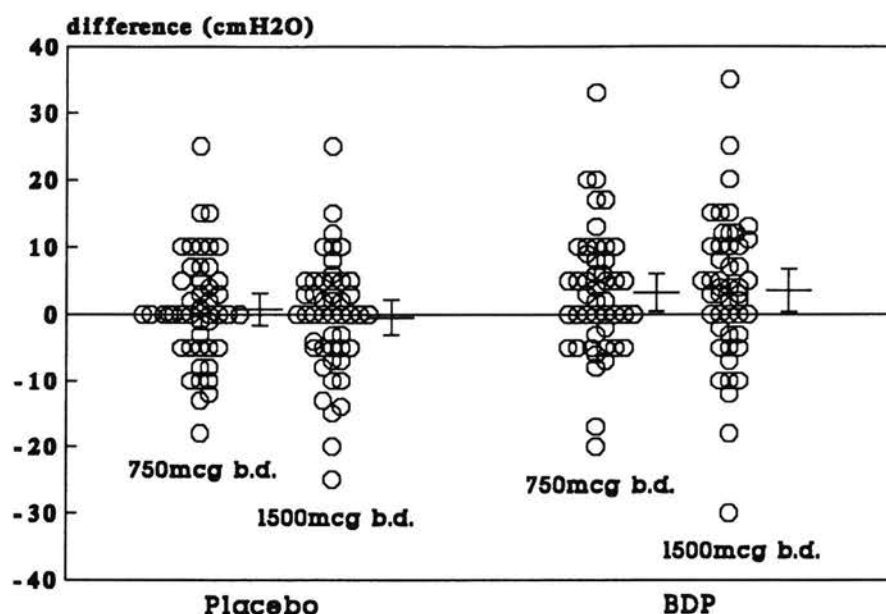


Figure 9.1. The change from baseline in Pimax after placebo and inhaled beclomethasone in individual patients for the two BDP dose groups. Error bars show mean change and 95% confidence interval for mean.

### 9.2.3. The effect of oral prednisolone.

#### *a. Maximal inspiratory mouth pressure.*

In the thirty one patients who continued on inhaled beclomethasone alone for the final treatment phase, there was no significant change in maximal inspiratory mouth pressure (both dose groups combined). The mean change (95% CI) from the value recorded after three weeks inhaled beclomethasone was 0.5 (-2.2 to 3.2) cmH2O. In the 59 patients who received oral prednisolone in addition to inhaled BDP, Pimax improved by a mean (95% CI) of 2.02 (-0.8 to 4.8) cmH2O, not statistically significant. The difference between the two final phase treatment groups was not statistically

significant ( mean [95% CI] difference 1.5 [5.8 to -2.7] cm H<sub>2</sub>O,  $t=-0.8$ , DF=84.2, ns).

*b. Maximal expiratory mouth pressure.*

Pemax improved in the 31 patients continuing on inhaled beclomethasone by a mean (95% CI) of 2.5 (-3.4 to 8.3) cmH<sub>2</sub>O, non significant. However the 58 patients who received oral prednisolone and inhaled beclomethasone for the final treatment phase showed a small but significant improvement in maximal expiratory mouth pressure ( mean (95% CI) 8.4 (3.5 to 13.2) cmH<sub>2</sub>O,  $p<0.001$ ). The difference between the groups did not reach statistical significance (mean [95% CI] difference 5.9 (13.7 to -1.8) cmH<sub>2</sub>O,  $t=-1.52$ , DF=87, ns).

### 9.3. DISCUSSION.

The measurement of maximal static mouth pressures is a valid and sensitive index of global respiratory muscle dysfunction(199). Initial reports of respiratory muscle function in chronic airflow obstruction suggested that muscle strength was increased compared to normal(200). However as subsequent investigators have pointed out these conclusions were erroneous as the normal ranges for respiratory muscle strength used were uncorrected for the effect of the static recoil of the respiratory system at high lung volumes. This tends to decrease the measured inspiratory muscle strength when measured at high lung volumes, and correcting for this suggests the initial report showed similar respiratory muscle strength in normals and patients with chronic airflow obstruction(201). Subsequent reports however, have concluded that both maximal inspiratory mouth pressure, and maximal expiratory mouth pressure are reduced in patients with significant chronic airflow obstruction(201,202,203,204).

The reason for the reduced muscle strength seen appears to be a combination of local mechanical and generalised nutritional factors. The airflow obstruction of chronic obstructive pulmonary disease produces hyperinflation of the lungs which causes shortening of the inspiratory muscles and places them at a mechanical disadvantage(205). Such mechanical considerations do not apply to the expiratory muscles, and some investigators have found a correlation between body mass and maximal mouth pressures(204,206), although others find no relationship at all(207).

The results of this study show baseline values of both maximal inspiratory mouth pressure, and maximal expiratory mouth pressure which are lower than the published normal ranges(208,209). A weak correlation between Pimax and hyperinflation as measured by the RV/TLC ratio was apparent, patients with higher ratios, ie more hyperinflation showing reduced inspiratory muscle strength. Both Pimax and Pemax showed a correlation with the mean PEF recorded over the week preceding the measurement, and in this group of patients body mass index, an

index of nutritional status, showed a correlation with expiratory muscle strength.

Myopathy of the skeletal muscles is a recognised complication of an excess of glucocorticoid, either endogenous or exogenous(210,211). Myopathy of the respiratory muscles has been described in case reports of patients with connective tissue diseases receiving high dose oral prednisolone(212), and in patients requiring ventilation for status asthmaticus(213,214). However in the first report it is possible that the underlying disease was responsible at least in part for the respiratory muscle weakness seen, and in the two asthmatics the doses of hydrocortisone used to treat the asthma were excessive. Whether oral or inhaled corticosteroid therapy in patients with no other cause for respiratory muscle weakness can cause a myopathy of the respiratory muscles is not clear.

Surveys of asthmatics treated with varying doses of oral corticosteroids have reached differing conclusions with regard to skeletal muscle myopathy. Bowyer et al found detectable weakness of the hip flexor muscles in asthmatics receiving greater than 40mg oral prednisolone per day(215). A more recent study in asthmatics treated with lower doses of oral prednisolone, a mean of 13 mg per day for nearly 10 years, detected no myopathy of skeletal or respiratory muscles(216).

A number of workers have examined the effect of glucocorticoids in animals, and usually have detected weakness and/or biochemical or histological changes of myopathy(217,218), usually within two weeks of the start of treatment. However the majority of such studies have used doses of corticosteroids far in excess of those used therapeutically in humans, and there may well be species differences in the susceptibility to steroid myopathy.

A study on normal human subjects published whilst this work was in progress provides more relevant information. In a parallel group study of 16 normal subjects no effect of oral prednisolone 20 mg per day for 2 weeks on respiratory muscle strength or endurance was noted(219). However there is a lack of information on the dose response characteristics and time course of the development of



corticosteroid myopathy and it is possible a longer period of treatment or a higher dose would induce detectable myopathy.

The current study has investigated a slightly longer treatment period and a higher dose of oral prednisolone, and also the effects of high dose inhaled corticosteroid over six weeks. The doses of inhaled beclomethasone used do produce systemic side effects, as judged by adrenal suppression (*vide infra*) and changes in calcium metabolism(220,221), so it is plausible that they may also produce effects on muscles.

The results show no detrimental effects of either six weeks treatment with inhaled beclomethasone, or three weeks treatment with both oral prednisolone and inhaled beclomethasone. Indeed Pimax improved after three weeks treatment with inhaled beclomethasone, and Pemax showed a small increase in the patients who received oral prednisolone for the final treatment phase. The magnitude of these change was small and would not be of clinical significance. The improvement in Pimax after three weeks treatment with inhaled beclomethasone may have been due to a continued learning effect rather than a true effect of treatment. However irrespective of any methodological problems the study was unable to show any untoward effect of treatment with both oral and inhaled corticosteroids over the short term. Whether long term treatment with high dose inhaled corticosteroids is at risk of inducing either skeletal or respiratory muscle myopathy will only be answered by further prospective studies.

## ***10. BRONCHIAL RESPONSIVENESS TO ULTRASONICALLY NEBULISED DISTILLED WATER AND PREDICTION OF RESPONSE TO INHALED BECLOMETHASONE IN PATIENTS WITH CHRONIC AIRFLOW OBSTRUCTION.***

### **10.1 ANALYSIS.**

Response to ultrasonically nebulised distilled water in the 49 patients tested was not normally distributed, and hence for all analysis in which response to ultrasonically nebulised distilled water was entered as a continuous variable a logarithmic transformation was used. Patients with a PD20 to ultrasonically nebulised distilled water of less than 2ml water were classified as responsive to ultrasonically nebulised distilled water(120), and those with values above this level as non responders to ultrasonically nebulised distilled water.

Comparisons of the baseline characteristics of the two ultrasonically nebulised distilled water response groups was carried out using an unpaired *t* test, and chi squared test where appropriate. To ensure patients in whom ultrasonically nebulised distilled water responsiveness was measured were representative of the whole study group, the baseline characteristics of those in whom the test was performed were compared by an unpaired *t* test and chi squared test to the patients who did not undergo this test.

The role of responsiveness to ultrasonically nebulised distilled water in predicting an individuals response to inhaled and oral corticosteroids was assessed by a variety of ways. The response to both active treatments was compared in the two ultrasonically nebulised distilled water response groups defined above by a chi squared test. In addition the change in FEV1, FVC and mean PEF after each treatment was correlated in individual patients with the measured responsiveness to ultrasonically nebulised distilled water. Finally as a secondary analysis the response to ultrasonically nebulised distilled water was entered as one factor in a discriminant analysis.

Prediction of response to inhaled beclomethasone in an individual was assessed by comparing baseline characteristics, including answers to the baseline questionnaire, in the beclomethasone responders and non responders, using an unpaired *t* test, and a chi squared test as appropriate. In addition a discriminant analysis was carried out on a cohort of similar patients who underwent a comparable trial 4 to 6 years previously. The results of this trial have been published(95). The analysis was performed using SPSS-PC, in a stepwise manner. The discriminant function obtained was applied to the current study group, and a new discriminant function was developed using variables that had not been measured in the first study.

## **10.2. RESULTS.**

### **10.2.1. Bronchial responsiveness to ultrasonically nebulised distilled water.**

Forty nine patients had bronchial responsiveness to ultrasonically nebulised distilled water (PD20 USDW) determined. There were no significant differences between the baseline characteristics of these 49 patients and the 25 patients who had bronchial responsiveness to inhaled histamine measured but not bronchial responsiveness to ultrasonically nebulised distilled water (table 10.1).

In 38 patients the FEV1 fell to less than 80% of the pre challenge value before 380 litres of nebulised mist had been delivered to the patient. In the remaining 11 patients the FEV1 did not fall by 20%, even after 380 litres of mist had been delivered. These patients had censored values, and in order that the maximum amount of data be available for analysis, where correlations were measured the non parametric Spearman's rho was utilised, with PD20 USDW entered as the untransformed value. The distribution of PD20 values to ultrasonically nebulised distilled water is shown in figure 10.1.. Fourteen patients had a PD20 USDW of less than 2ml water and were classified as responsive to ultrasonically nebulised distilled water.

Statistically significant correlations were found between PD20 USDW and the degree of airflow obstruction, as measured by the FEV1 and FEV1/FVC ratio, but not with mean baseline PEF, diurnal variation in PEF or reversibility to 200 mcg salbutamol (table 10.2.). Significant correlations were also seen between the bronchial responsiveness to ultrasonically nebulised distilled water, and that measured to inhaled histamine by both of the methods used.

Table 10.1. Characteristics of patients in whom bronchial responsiveness to ultrasonically nebulised distilled water was measured (USDW +), and in those in whom only bronchial responsiveness to inhaled histamine was determined (USDW -). As mean (95% CI), or number.

	USDW +	USDW -
Number (female)	49 (9)	25 (7)
Age (yrs)	67 (65 to 68)	64 (61 to 67)
Mean FEV1 (l) <i>as % predicted</i>	1.3 (1.2 to 1.4) 48 (45 to 51)	1.15 (1.0 to 1.3) 43 (38 to 49)
Mean FVC (l) <i>as % predicted</i>	2.8 (2.5 to 3.0) 86 (82 to 90)	3.0 (2.8 to 3.2) 83 (78 to 89)
Mean FEV1/FVC (%)	45 (42 to 48)	42 (37 to 47)
Mean PEF (l/min)	269 (247 to 292)	262 (228 to 296)
FEV1 reversibility to 200 mcg salbutamol as absolute (ml)	134 (90 to 179)	158 (102 to 213)
% pred FEV1	6.2 (3.9 to 8.5)	4.8 (3.1 to 6.5)
Geometric mean PD20 histamine (umol)	0.59	0.41
Smoking status [as number (%)]		
Current	24 (49)	11 (44)
Ex smokers	25 (51)	13 (52)
Never	0	1 (4)
Number(%) skintest positive	12 (24)	4 (16)

'Mean' refers to mean baseline values.

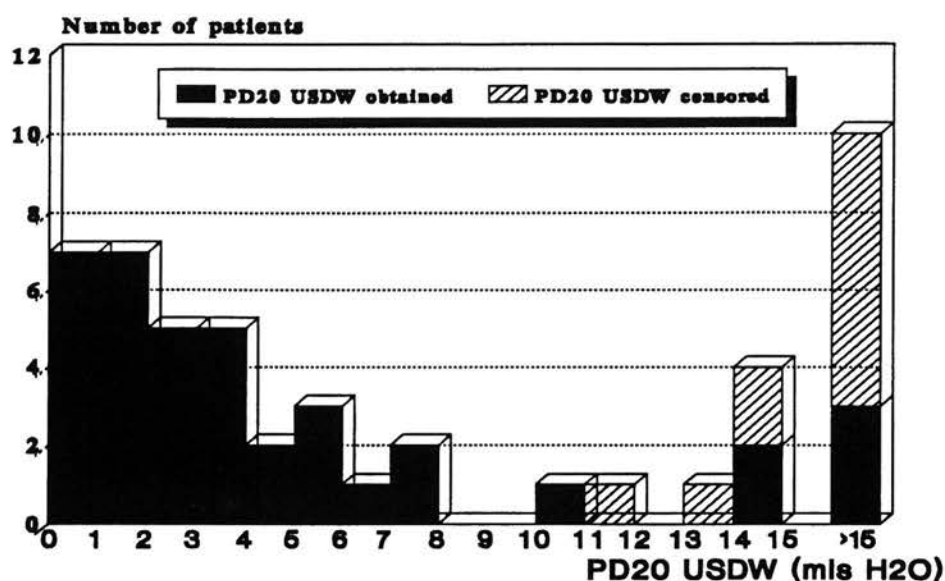


Figure 10.1. Distribution of PD20 USDW values for the 49 patients who had this measured. In 11 patients the value was censored, and in these cases the amount of ultrasonically nebulised distilled water inhaled is indicated.

Table 10.2. Spearman rank correlation coefficients between PD20 USDW and various measures of lung function in the 49 patients.

	Spearman rho
FEV1 (l)	0.51 **
FEV1/FVC (%)	0.33 *
Mean baseline PEF (l/min)	0.16
PEF diurnal variation (as % mean PEF)	-0.24
Reversibility to 200 mcg salbutamol as absolute change (ml)	0.16
as % predicted FEV1	0.13
Bronchial responsiveness to histamine	
PC20 (Yan method) (umol)	0.57 **
PD20 (Cockcroft method) (mg/ml)	0.54 **

\*\*  $p < 0.05$ . \*  $p < 0.01$ .

Patients who were classified as responsive to a mist of ultrasonically nebulised distilled water, ( a PD20 USDW of less than 2ml water), had more severe airflow obstruction and were more responsive to inhaled histamine than the remaining 35 patients unresponsive to the mist (table 10.3.).

Of the 49 patients who had bronchial responsiveness to ultrasonically nebulised distilled water measured, eleven showed a response to inhaled beclomethasone as defined (an improvement in FEV1, FVC or mean PEF of at least 20% compared to baseline values). There was no difference in the response rate to inhaled beclomethasone in the two ultrasonically nebulised distilled water response groups (figure 10.2.).

The correlation between the change in FEV1, FVC and mean PEF from baseline, after inhaled beclomethasone, and PD20 USDW was poor (table 10.4.). No statistically significant associations were seen.



Table 10.3. The baseline characteristics of the two ultrasonically nebulised distilled water response groups. As mean (95% CI) unless indicated.

	USDW Responders	USDW Non Responders
Number (female)	14 (3)	35 (6)
Age (years)	66 (63.3 to 69)	67 (64.4 to 69.1)
FEV1 (litres)	1.10 (0.9 to 1.3)	1.39 * (1.27 to 1.5)
FEV1 (% predicted)	43.3 (35.9 to 50.6)	49.7 (46.0 to 53.4)
FEV1/FVC %	39.0 (32.9 to 45.2)	46.4 * (42.8 to 49.8)
Mean PEF (l/min)	249 (206 to 292)	278 (250 to 305)
Diurnal variation in PEF (% mean)	23.7 (15.8 to 31.6)	17.6 (14.6 to 20.5)
FEV1 reversibility to 200mcg salbutamol as absolute change (ml)	129 (15 to 243)	137 (89 to 183)
% predicted FEV1	4.8 (0.5 to 9.1)	4.8 (3.0 to 6.7)
Geometric mean PD20 histamine (Yan)(umol)	0.33	0.97 *
Smoking status,as number(%)		
Current	8 (57)	16 (46)
Ex	6 (43)	19 (54)
Number with positive skin tests (%)	2 (14)	10 (29)

\*  $p < 0.05$  for comparison by unpaired Student *t* test.

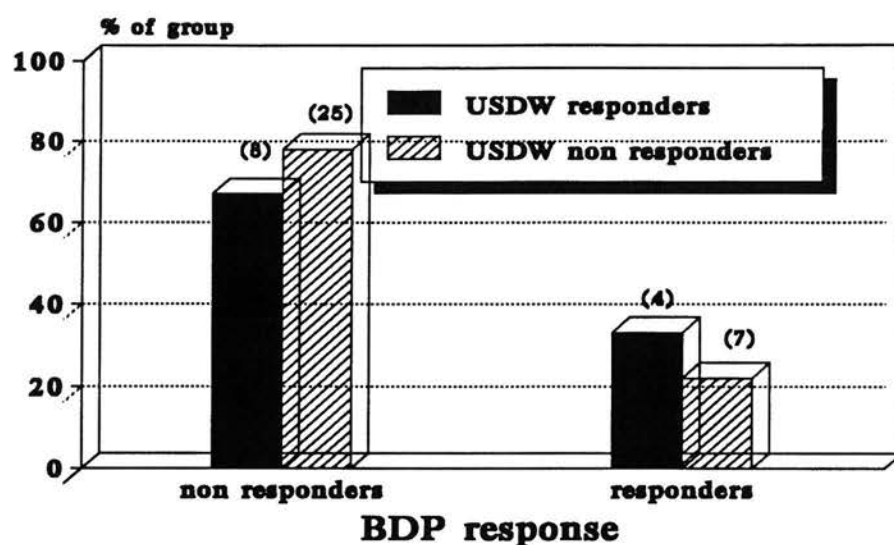


Figure 10.2. The percentage of patients in each ultrasonically nebulised distilled water response group showing a response to inhaled beclomethasone after the first active treatment phase.

Table 10.4. Spearman rank correlation coefficients between PD20 USDW and the change in FEV1, FVC and mean PEF from baseline after treatment with inhaled beclomethasone from the first active treatment phase.

	Spearman rho
FEV1 (l)	-0.11
FVC (l)	-0.02
Mean PEF (l/min)	-0.05

### **10.2.2. Prediction of response to inhaled beclomethasone dipropionate.**

The differences in baseline characteristics between the 33 patients classified as responders to inhaled beclomethasone after the first active treatment phase and the non responders are tabulated in tables 10.5 to 10.8. Response to inhaled beclomethasone was defined as an increase in FEV1, FVC or mean PEF of at least 20% compared to baseline values.

Responders to inhaled beclomethasone had significantly greater airflow obstruction as measured by FEV1, more hyperinflation of the lungs as indicated by the raised functional residual capacity, residual volume and total lung capacity. There were no significant differences in measures of allergy, ie; skin test reactivity or serum IgE level, between the inhaled beclomethasone response groups. Similarly the answers to selected questions from the baseline respiratory symptom questionnaire showed no difference between the two response groups.

Correlations between baseline physiological variables and the absolute change, from baseline values, in FEV1, FVC, and mean PEF after three weeks treatment with inhaled beclomethasone are shown in table 10.9.. The correlations were of a low order, and in most cases failed to reach conventional levels of statistical significance.

Table 10.5. Baseline spirometric measurements, peak expiratory flow variability, reversibility of FEV1, and bronchial responsiveness to inhaled histamine and ultrasonically nebulised distilled water in the two beclomethasone response groups. As mean (95% CI) unless indicated.

	Non Responders	Responders
Number (female)	65 (17)	33 (12)
Age (years)	65.6 (63.8-67.3)	66.3 (64.5-68.1)
Mean FEV1 (l) <i>as % predicted</i>	1.13 (1.01-1.25) 42 (39-46)	0.91 (0.75-1.07) * 36 (31-41) *
Mean FVC (l) <i>as % predicted</i>	2.78 (2.58-2.97) 82 (78-86)	2.47 (2.19-2.74) 78 (72-83)
Mean FEV1/FVC %	41 (38-44)	36 (32-41)
Mean PEF (l/min) <i>as % predicted</i>	241 (219-264) 55 (51-59)	219 (186-252) 52 (46-57)
Diurnal variation in PEF <i>as % mean</i> <i>as % pred</i>	21 (18-24) 11 (10-13)	21 (18-25) 10 (9-11)
FEV1 reversibility to 200mcg salbutamol absolute (ml) % pred FEV1	137 (106-169) 5.3 (4.0-6.5)	177 (126-177) 7.3 (5.3-9.4)
Geometric mean PD20 histamine (umol)	0.59	0.40
Geometric mean PD20 USDW (ml H2O)	4.95	4.26

\*  $p < 0.05$  by unpaired  $t$  test.

Values for FEV1, FVC, and FEV1/FVC ratio are the mean of the three baseline measurements.

For definition of indices of reversibility and diurnal variation see Methods.

Table 10.6. Results of static lung volumes and carbon monoxide gas transfer measurements at baseline in the two inhaled beclomethasone response groups. As mean (95% CI) unless indicated.

	Non Responders (n=65)	Responders (n=33)
FRC (litres) <i>as % predicted</i>	4.54 (4.24-4.83) 139 (132-147)	4.82 (4.47-5.17) 154 (144-164) *
RV (litres) <i>as % predicted</i>	3.52 (3.27-3.77) 154 (144-165)	3.83 (3.50-4.16) 173 (158-188) *
TLC (litres) <i>as % predicted</i>	6.34 (6.0-6.71) 106 (101-110)	6.47 (6.02-6.92) 114 (108-120) *
Mean TLCO (mmol/min/kPa) <i>as % predicted</i>	5.7 (5.1-6.2) 71 (64-77)	5.0 (4.1-5.9) 65 (55-74)
Mean KCO (mmol/min/kPa/l) <i>as % predicted</i>	1.07 (0.98-1.17) 60 (55-66)	0.98 (0.83-1.13) 55 (46-64)

\*  $p < 0.05$  by unpaired Student *t* test.

Values for carbon monoxide gas transfer (TLCO) and the KCO carbon monoxide gas transfer coefficient (KCO) are the mean of the two baseline values.

Table 10.7. Details of markers of allergy, and smoking history of the two inhaled beclomethasone response groups. As mean (95% CI) unless indicated.

	Non Responders (n=65)	Responders (n=33)
WCC ( $\times 10^9/l$ )	7.7 (7.2-8.2)	7.7 (7.1-8.3)
Eosinophil count ( $\times 10^9/l$ )	0.12 (0.08-0.16)	0.17 (0.12-0.22)
Geometric mean serum IgE (ku/l)	83	55
Number with positive skin tests (%)	15 (23)	5 (33)
Cigarette consumption (pack years)	52 (44-61)	42 (32-51)
Smoking status [as number (%)]		
Current	34 (52)	11 (33)
Ex	30 (46)	22 (67)
Never	1 (2)	0 (0)

WCC- peripheral white blood cell count.  
No significant differences between groups.

Table 10.8. Answers to selected questions from the baseline respiratory symptom questionnaire in the two inhaled beclomethasone response groups. Expressed as the number (% of response group) giving a positive answer unless indicated otherwise.

	Non Responders	Responders
Chronic bronchitis	44 (68)	22 (67)
Breathlessness score		
0	22 (34)	13 (39)
1	15 (23)	8 (24)
2	23 (35)	10 (30)
3	5 (8)	2 (6)
Are you worse in any one season than another ?	34 (54)	12 (36)
Ever wheezy or whistling ? (question 15)	57 (88)	29 (88)
Possible 'asthma' (questions 16 & 17)	23 (35)	10 (30)
Prolonged morning chest tightness (> 60 minutes) (question 23 & 24)	16 (25)	6 (18)
Bronchial irritability	28 (43)	11 (33)
Positive answers to		
'Have you ever had -		
bronchitis	47 (72)	22 (67)
bronchial asthma	11 (17)	4 (12)
hay fever	6 (9)	3 (9)
eczema	8 (12)	3 (9)

No significant differences.

For definition of possible 'asthma', bronchial irritability, and breathlessness scores see Methods.



Table 10.9. Correlation coefficients between various baseline physiological variables and the change from baseline in FEV1, FVC and mean PEF following treatment with inhaled beclomethasone.

	FEV1	CHANGE IN FVC	mean PEF
FEV1 reversibility to 200mcg salbutamol as absolute change	0.05	-0.07	0.20*
as % pred	0.03	-0.05	0.20*
Diurnal variation in PEF as % mean	-0.02	-0.01	-0.05
as % predicted PEF	0.03	-0.02	-0.02
logPD20	-0.20	-0.20	-0.01
PC20 to ultrasonically nebulised distilled water	-0.11	-0.02	-0.05
log <sub>10</sub> IgE	-0.03	-0.13	-0.03
Pack years	0.01	0.10	-0.23*
TLCO	-0.12	-0.27**	0.08

\*  $p < 0.05$ , \*\*  $p < 0.01$ .

Pearson correlation coefficients are shown for all except PC20 to ultrasonically nebulised distilled water, where Spearman's rho is given.

logPD20 = bronchial responsiveness to inhaled histamine by the method of Yan.

Pack years = cigarette consumption.

TLCO = carbon monoxide gas transfer.

A discriminant function to predict response to inhaled beclomethasone was derived using the database from a previous study(95). The baseline characteristics of this patient group are given in table 10.10.

Table 10.10. Baseline characteristics of the patients from the earlier study(95), used to develop the discriminant function. As mean (SEM) unless indicated.

Number (females)	107 (25)
Age (years)	62.9 (0.9)
FEV1 (litres) (as % predicted)	1.19 (0.04) 44 (1.6)
FVC (% predicted)	79 (1.8)
TLC (% predicted)	122 (1.9)
RV (% predicted)	174 (5.0)
TLCO (% predicted)	78 (3.1)
Mean PEF (% predicted)	52 (1.7)
Diurnal variation in PEF (% mean)	19.8 (1.0)
FEV1 reversibility to 200 mcg salbutamol as absolute change (ml) as % predicted	132 (13) 4.7 (0.4)
Smoking status [ as number (%)]	
Current	41 (38)
Ex	54 (50)
Never	12 (12)
Cigarette consumption (pack yrs)	38 (2.6)
Serum IgE (ku/l) as geometric mean (range)	74 (3-4500)
Skin test positive (no [%])	46 (43)

Exploratory analyses were performed to assess the possible significance of various variables, and finally the following variables were selected from which to define a discriminant function.

1. age (years);
2. sex ( as a dichotomous variable);
3. FEV1 (in litres);
4. FVC (in litres);
5. KCO -the carbon monoxide gas transfer coefficient (as percentage of the predicted value);
6. TLC -total lung capacity (as percentage of the predicted value);
7. RV -residual volume (as percentage of the predicted value);
8. PEF diurnal variation as a percentage of the mean PEF;
9. FEV1 reversibility to 200 mcg salbutamol, expressed as percentage of the predicted FEV1 value (% pred);
10. PC20 histamine, entered after logarithmic transformation;
11. Serum IGE level, entered after logarithmic transformation;
12. Skin test reactivity, 0=negative, 1=positive;
13. Smoking status, entered as two variables, variable 1 1=current and ex smoker, 0=never smoker; variable 2 1=current smoker, 0=ex and never smokers.
14. Answer to the question 'Do you wheeze on going from warm to cold air ?' 0=no, 1=yes.
15. Answers to the questions 'Have you ever had attacks of shortness of breath with wheezing ?', and 'Was your breathing absolutely normal between attacks ?' (asthma?) 1=positive answers to both questions, 0=either question answered no.

Seventy three of the 107 cases had complete data and were used in defining the discriminant function. The final function correctly classified 65% of the cases. The discriminant function derived was,

$$(0.056 \times \text{age}) + (0.67 \times \log \text{IgE}) + (1.06 \times \text{smoking [variable 2]}) - (0.98 \times \text{sex}) - (0.39 \times \text{asthma}) - (0.75 \times \text{skin test}) - 3.64.$$

(Scores of less than zero indicated non responders to inhaled beclomethasone, above zero responders).

The other variables, including all physiological variables used, did not significantly improve the prediction of corticosteroid response in this patients group.

This discriminant function was used to predict response to 3

weeks treatment with inhaled beclomethasone in the current patient cohort. Unfortunately the function proved to be a poor discriminator. Although only six of the 33 actual responders to inhaled beclomethasone were not identified correctly by the discriminant function, 55 of the 65 patients who showed no response to inhaled beclomethasone were assigned to the response group by the discriminant function.

The data generated by the current study was then used to define a second discriminant function to predict response to inhaled beclomethasone. For this exercise analyses were carried out using various combinations of the baseline variables. In all analyses bronchial responsiveness to ultrasonically nebulised distilled water did not enter the final predictor equation.

The 'best' equation obtained was

$$(0.012 \times \text{pack years}) + (1.01 \times \text{smoking variable 2}) + (0.057 \times \text{FVC}) + (0.073 \times \text{SVC}) + (0.075 \times \text{RV}) + (0.72 \times \text{bronchial irritability}) - (3.56 \times \text{smoking variable 1}) - (0.18 \times \text{TLC}) - (0.027 \times \text{FRC}) + 3.29.$$

(Scores of less than zero indicated non responders to inhaled beclomethasone, above zero responders).

Where ;

pack years = cigarette consumption,

smoking status entered as above,

FVC, TLC, SVC, FRC, RV are entered as percentage of predicted values,

bronchial irritability as defined above (page 65).

This discriminant correctly classified 74% of the patient population from which it was derived. If only patients scoring over 1 were given a 'trial of steroids', only 38 patients would be tested. Of these 23 would respond to inhaled beclomethasone, but 10 inhaled beclomethasone responders would not be offered a 'trial of steroids'.

### 10.3. DISCUSSION.

#### *a. Bronchial responsiveness to ultrasonically nebulised distilled water.*

Bronchial responsiveness to ultrasonically nebulised distilled water has been investigated fairly extensively in asthma, but there has been little published work on the response of the bronchi in patients with chronic airflow obstruction to the same stimulus.

The characteristics of bronchial responsiveness to hypotonic and hypertonic aerosols in asthma has been reviewed by Anderson(120,222). The test appears to be reproducible over time(223), but is less sensitive than metacholine challenge testing in detecting asthma. In 89 patients with symptoms of asthma, 11 had a PD<sub>20</sub> USDW of over 15ml water whereas all patients showed bronchial hyperresponsiveness to inhaled metacholine within the asthmatic range(223). Significant correlations were seen in this study and another(224) between bronchial responsiveness to metacholine and ultrasonically nebulised distilled water.

It has been suggested that bronchial hyperresponsiveness to ultrasonically nebulised distilled water is specific for asthma. Whilst it is possible to induce bronchoconstriction in normal subjects to either histamine or metacholine provided a large enough dose is given(107), it is unusual to see a response to ultrasonically nebulised distilled water in normal subjects. Anderson's study failed to elicit a response in 12 normal subjects(224), and in a larger study only 1 of 26 normal or 'allergic' subjects reacted to ultrasonically nebulised distilled water(225).

The response to ultrasonically nebulised distilled water in asthma is blocked by sodium cromoglycate, and shows tachyphylaxis(223), suggesting the mechanism involved is not a direct action on bronchial smooth muscle. After bronchoconstriction induced by ultrasonically nebulised distilled water plasma histamine levels increase, and the neutrophil chemotactic activity of serum is enhanced(226). In addition, in asthmatics challenge of isolated airway segments with hypotonic solutions results in the release of mast cell mediators(227), suggesting the main effect of such

challenges is via the mast cell population of the bronchi.

Although bronchial hyperresponsiveness to ultrasonically nebulised distilled water has been claimed to be specific to asthma, there are reports of bronchoconstriction in response to hypo- and hypertonic aerosols in patients with non asthmatic chronic airflow obstruction. These reports suffer from poor patient characterisation, and use challenge methods which are cruder than that developed by Anderson, but there appears to be no doubt that ultrasonically nebulised distilled water can induce bronchoconstriction in patients with airflow obstruction not due to asthma. Cheney and Butler showed an increase in airways resistance in ten patients with chronic bronchitis after inhalation of mists of distilled water, half normal saline, and normal saline(228). Another study in thirty patients with chronic bronchitis and airflow obstruction showed a hypotonic solution, 0.45% sodium chloride, caused a fall in FEV1 and FVC, and in some patients a fall in arterial blood gas tensions(229). A further study confirmed the changes seen in arterial blood gas tensions, on this occasion after nebulisation of normal saline(230). Other workers found an increase in airway resistance and a fall in FEV1 following inhalation of ultrasonically nebulised distilled water in patients with chronic airflow obstruction(231). More recently Anderson et al have confirmed that a proportion of patients with chronic airflow obstruction not due to asthma do show bronchoconstriction after inhalation of non isotonic solutions(232).

Our results confirm that some patients with chronic airflow obstruction, not clinically asthmatic, develop bronchoconstriction in response to the inhalation of ultrasonically nebulised distilled water. In our group the proportion in whom the FEV1 falls by at least 20% is higher (77%) than that seen in Anderson's study (65%)(233). A moderate, albeit statistically significant, correlation was seen between bronchial responsiveness to the osmotic stimulus and that measured to inhaled histamine, by either of the methods used. The degree of correlation was similar to that seen in asthma between ultrasonically nebulised distilled water and metacholine by Anderson's group ( $r=0.6$ )(223), and in Hopp et al's study ( $r=0.62$ )(226).

Although a high percentage of the study group reacted to ultrasonically nebulised distilled water, it is possible that bronchial hyperresponsiveness to ultrasonically nebulised distilled water is an indicator of 'asthmatic' airflow obstruction. However our results do not support this. The correlation between diurnal variation in PEF, and FEV1 reversibility to beta 2 agonists, often considered markers of and used to define asthma, was poor. The strongest correlation was between the degree of airflow obstruction, as measured by the FEV1, and bronchial responsiveness to ultrasonically nebulised distilled water. This suggests that in the patients studied the strongest determinant of an individuals response to ultrasonically nebulised distilled water are geometric factors, as appears to be the case with responsiveness to inhaled histamine.

In addition if as many authorities believe a response to inhaled beclomethasone over the three week treatment period indicates a predominantly 'asthmatic' element to the airflow obstruction, then patients who show bronchial hyperresponsiveness to ultrasonically nebulised distilled water should show a greater response to treatment with the inhaled corticosteroid. However this was not found to be the case. The response rate to inhaled beclomethasone in the two 'mist' response groups was similar, and the correlation between PD20 to ultrasonically nebulised distilled water and the change in FEV1, FVC or mean PEF after treatment was poor. Hence the hypothesis that bronchial responsiveness to ultrasonically nebulised distilled water could be used to select patients more likely to respond to corticosteroids is not supported by this study.



***b. Prediction of response to inhaled beclomethasone dipropionate.***

It was not possible to predict response to inhaled beclomethasone in this group of patients. Both a simple comparison of physiological variables and symptoms, and the more complex discriminant analysis were unable to satisfactorily separate responders to inhaled beclomethasone from non responders.

Other studies have also attempted to identify features which may indicate a likely response to corticosteroids, but only the study of Harding and Freedman(100), used an inhaled corticosteroid as the treatment. They reported that patients with eosinophilia in the peripheral blood were more likely to show a response to corticosteroids, but found no effect of a personal or family history of allergy, skin test reactivity, or bronchodilator responsiveness on steroid responsiveness. The features considered by other authors, and the results are tabulated below in table 10.11..

The results of this study indicate that responders to inhaled beclomethasone had more severe disease, as indicated by a lower FEV1, a reduced FEV1/FVC ratio, and increased static lung volumes. The inverse association between the starting level of FEV1, and the response rate to corticosteroids has been commented upon before(85). The likeliest explanation is that most studies, as the current one, have used percentage change in FEV1 to define response to treatment. This means that patients with more severe airflow obstruction need show a smaller absolute increase in the variable after treatment to be classed as a responder, and hence these patients are preferentially selected for the response group.

Peak flow variability, measured as the diurnal variation in PEF, and reversibility of airflow obstruction are often used to define asthma(182,183). In this study the two inhaled beclomethasone response groups showed similar levels of variability in PEF. Although responders did show greater FEV1 reversibility, the difference did not reach statistical significance because of the wide range of values seen. This criteria would not reliably separate response groups.

Table 10.11. Studies showing positive or negative associations between various features and steroid response. Studies indicated by reference number.

	Positive	Negative
Bronchodilator response	88,89,91.	66,74,83,90,95,100.
Blood eosinophilia	71,100.	88,89,90,92.
Sputum eosinophilia	88.	89,90,92.
Family or personal history of allergic disease	69,71.	81,92,100.
Positive skin tests	71.	90,92,100.
Increased serum IgE level	-	90,92.
Reduced TLCO	-	91.
Bronchial hyperresponsiveness to histamine	-	74.

TLCO carbon monoxide gas transfer.

Bronchial hyperresponsiveness to inhaled histamine is present in both asthma and chronic airflow obstruction, where it probably reflects different underlying pathogenic mechanisms. Bronchial responsiveness to inhaled histamine or ultrasonically nebulised distilled water was not different between inhaled beclomethasone response groups.

Allergic features have previously been suggested as indicative of response to corticosteroids. In this study this was not the case. Although the responders to inhaled beclomethasone had a higher blood eosinophil count, there was a wide overlap between the two inhaled beclomethasone response groups. Non responders showed a slightly higher serum IgE level, the percentage of each response

group with positive skin tests was comparable, and similar numbers reported a history of allergic disease. Despite previous reports allergic features did not predict response to corticosteroids in this study.

It is of interest that the discriminant function derived from the database of the earlier study included three variables which may reflect underlying allergy, ie; serum IgE level, skin test reactivity, and attacks of wheezing with normal breathing in between attacks. The lack of any difference between response groups in these variables in the present study probably explains the poor predictive value of the discriminant function derived. The population from which the discriminant function was derived had more skin test reactors, and a higher mean serum IgE level, and had smoked less than the current study population. This suggests the population may have inadvertently included missed asthmatics, and hence the discriminant function may only be applicable to a similar patient population. It also suggests that previous studies which have shown 'asthmatic' features to be predictive of a response to corticosteroids have probably also included some undiagnosed asthmatics in the population studied.

Mortagy et al suggested that the presence of their bronchial irritability syndrome should alert the clinician to the possible benefits of treatment with corticosteroids(165). The results from my study suggest that in this group of patients the presence of bronchial irritability as defined dose not relate to response inhaled beclomethasone. The percentage of patients with this syndrome was similar in the two inhaled beclomethasone response groups. The answers to other questions did not reliably distinguish between the response groups either.

Bronchial irritability was one of the variables included in the second discriminant function derived from the current study database. The remaining variables included described either smoking status, or physiological measures. The final function only predicted three quarters of responders and non responders correctly. If used to select patients for a 'trial of steroids' nearly one third of

inhaled beclomethasone responders would not be identified. If applied to another population it is likely the ability of the discriminant function to predict inhaled beclomethasone response group would be less. The clinical usefulness of such a function is poor, but the difficulty obtaining an adequate function does illustrate the heterogeneous nature of the disease. It is probable that identification of short term response to corticosteroids will always require an empirical trial in all patients. The usefulness of identifying short term response to corticosteroids however is increasingly being questioned(234) (vide infra).

## **11. SIDE EFFECTS OF TREATMENT:**

### **A. HYPOTHALAMIC-PITUITARY-ADRENAL AXIS SUPPRESSION.**

### **B. LOCAL ORO-PHARYNGEAL EFFECTS**

**-CANDIDIASIS  
-DYSPHONIA.**

#### **11.1. ANALYSIS.**

The effect of treatment with inhaled beclomethasone and oral prednisolone on tests of hypothalamic-pituitary-adrenal (HPA) axis function has been assessed by analysing the change in;

- (a) the unstimulated pre tetracosactrin serum cortisol,
- (b) the stimulated post tetracosactrin cortisol, and
- (c) the increment in serum cortisol following tetracosactrin,
- (d) and the 24 hour urinary free cortisol measurement.

Although because of practical difficulties the timing of sample collection for the unstimulated cortisol was not standardised between patients, for individual patients the samples were collected at the same time of the day, hence a within patients assessment of effect of treatment is appropriate. Unfortunately interference from metabolites of prednisolone in the assay for urinary free cortisol, an unexpected problem, meant that urinary free cortisol measurements measured after the oral prednisolone phase gave unreliable estimates of cortisol excretion, and this data has not been analysed. A repeated measures analysis of variance, with dose of inhaled beclomethasone entered as a factor, was used to assess the effect of inhaled beclomethasone on the above parameters, and to look for any difference between the effect of the two dose of inhaled beclomethasone used. For the effect of the final phase of treatment on measures of HPA axis function, a paired *t* test was used to compare the values obtained after three weeks treatment with inhaled beclomethasone alone, to that measured after the final treatment phase, when two thirds of patients received oral prednisolone in addition to inhaled beclomethasone.

In addition the results of individual tests on patients were classified into 'passes' or 'failures' using predetermined criteria.

Both the post tetracosactrin serum cortisol and the increment in serum cortisol following tetracosactrin were used in this analysis. The criteria used were a post tetracosactrin serum cortisol level greater than 550 nmol/l, and an increment in serum cortisol at 30 minutes following injection of tetracosactrin of greater than 200nmol/l. The number of individuals failing each test after each active treatment was compared using a chi squared test, or a McNemar test as appropriate.

For the analysis of the oral candida scores, the number of patients with visible candidiasis, was compared with the number without visible candida, that is scores 0 to 2, and 3 and 4 were combined into two categories. The comparisons between scores on placebo and after inhaled beclomethasone, and between scores after the first three weeks of inhaled beclomethasone and those after the second active treatment phase in individual patients were carried out using McNemar's test. Differences in scores between the two beclomethasone dose groups after inhaled beclomethasone, and after the final treatment phase between those patients receiving oral prednisolone and those continuing on inhaled beclomethasone alone, were assessed by using a chi squared test. For the dysphonia scores a Wilcoxon signed rank test or Mann Whitney U test was used as appropriate.

## **11.2. RESULTS.**

### **11.2.1. HPA axis function.**

#### *a. Data collection.*

A number of patients declined to undergo venepuncture for the estimation of serum cortisol on each trial visit. As this was not the primary objective of the study these patients were allowed to continue in the remainder of the study. Two patients suffered vasovagal reactions following the slow intravenous injection of tetracosactrin and this test was not repeated in these two individuals.

Ninety eight patients had unstimulated cortisol values available for analysis at baseline and after inhaled beclomethasone. Post tetracosactrin levels were available after both phases in 87 patients, and urinary free cortisol measurements in 89 individuals.

After the final treatment phase unstimulated serum cortisol levels were available in 32 of the 33 patients who received inhaled beclomethasone only for this phase, and post tetracosactrin cortisol were measured in 28 of these patients. Urinary free cortisol levels were available in 29 of the patients receiving inhaled beclomethasone alone as the final treatment. In the patients receiving oral prednisolone in addition to inhaled beclomethasone, for the final treatment phase unstimulated serum cortisol levels were measured in 58 of the 65 patients, post tetracosactrin levels in 52 patients, and the urinary free cortisol estimations were not analysed because of interference in the assay.

#### *b. The effect of inhaled beclomethasone.*

There was no detectable effect of treatment with inhaled beclomethasone on unstimulated serum cortisol levels (table 11.1.). However the three other indices of HPA axis function showed significant suppression after treatment for three weeks with inhaled beclomethasone. The effect of the higher dose of inhaled beclomethasone was significantly greater for the post tetracosactrin cortisol and the increment in serum cortisol. Urinary free cortisol



levels were suppressed to a greater extent in the higher BDP dose group, but not significantly so. For the increment in serum cortisol following tetracosactrin, the effect of treatment in the 750mcg b.d. group was not statistically significant when assessed by a paired Student *t* test.

A further three weeks treatment with inhaled beclomethasone alone during the final treatment phase produced no further evidence of HPA axis suppression (table 11.2.).

The change from baseline after three weeks treatment with inhaled beclomethasone in unstimulated and post tetracosactrin serum cortisol levels is shown in figure 11.1..

Table 11.1. The mean (95% confidence limits for mean) for the results of the tests of HPA function, at baseline and after three weeks treatment with inhaled beclomethasone, in the two dose groups.

	Baseline	Post BDP
<i>Unstimulated cortisol.</i>		
750mcg b.d.(n=47)	382 (339-425)	357 (316-398)
1500mcg b.d.(n=51)	350 (309-390)	334 (291-378)
Treatment effect F-ratio=1.83, DF=1,ns. Interaction F-ratio=0.12, DF=1,ns.		
<i>Stimulated cortisol.</i>		
750mcg b.d.(n=43)	868 (822-913)	805 (766-844)
1500mcg b.d.(n=44)	866 (810-923)	704 (651-757)
Treatment effect F-ratio=38.9,DF=1,p<0.0001. Interaction F-ratio=7.55, DF=1,p<0.008.		
<i>Cortisol increment.</i>		
750mcg b.d.(n=43)	474 (432-517)	442 (411-473)
1500mcg b.d.(n=44)	514 (462-566)	376 (333-423)
Treatment effect F-ratio=24.5, DF=1,p<0.0001. Interaction F-ratio=9.33, DF=1,p<0.004.		
<i>Urinary free cortisol.</i>		
750mcg b.d.(n=41)	167 (138-195)	134 (112-156)
1500mcg b.d.(n=48)	152 (131-172)	90 (76-103)
Treatment effect F-ratio=33.5, DF=1,p<0.0001. Interaction F-ratio=3.05, DF=1,p=0.08.		

Unstimulated cortisol- pre tetracosactrin injection.

Stimulated cortisol- post tetracosactrin injection.

Increment- difference between stimulated and unstimulated levels.

Table 11.2. The mean values (95 % CI) and the mean difference (95 % CI) between values at three and six weeks, for the four tests of HPA function, in the patients who received beclomethasone alone for the final treatment phase, for the two BDP dose groups.

	3 weeks	6 weeks
Unstimulated cortisol.		
750mcg b.d.(n=16)	332 (274 to 389) ( mean difference -6.3 (-60 to 48), ns.)	338 (276 to 400)
1500mcg b.d.(n=16)	332 (263 to 402) ( mean difference -1.25 (-105 to 102), ns.)	334 (233 to 435)
Stimulated cortisol.		
750mcg b.d.(n=14)	806 (724 to 888) ( mean difference 15.3 (-78 to 108), ns.)	791 (691 to 890)
1500mcg b.d.(n=14)	684 (589 to 780) ( mean difference -34 (-142 to 73), ns.)	719 (600 to 837)
Cortisol increment.		
750mcg b.d.(n=14)	469 (413 to 525) ( mean difference 31.6 (-73 to 136), ns.)	438 (329 to 547)
1500mcg b.d.(n=14)	358 (262 to 454) ( mean difference 0.2 (-65 to 66), ns.)	358 (265 to 451)
Urinary free cortisol.		
750mcg b.d.(n=13)	157 (114 to 200) ( mean difference -17 (-74 to 39), ns.)	174 (113 to 235)
1500mcg b.d.(n=16)	85 (58 to 112) ( mean difference -25 (-51 to 1), ns.)	110 (78 to 141)

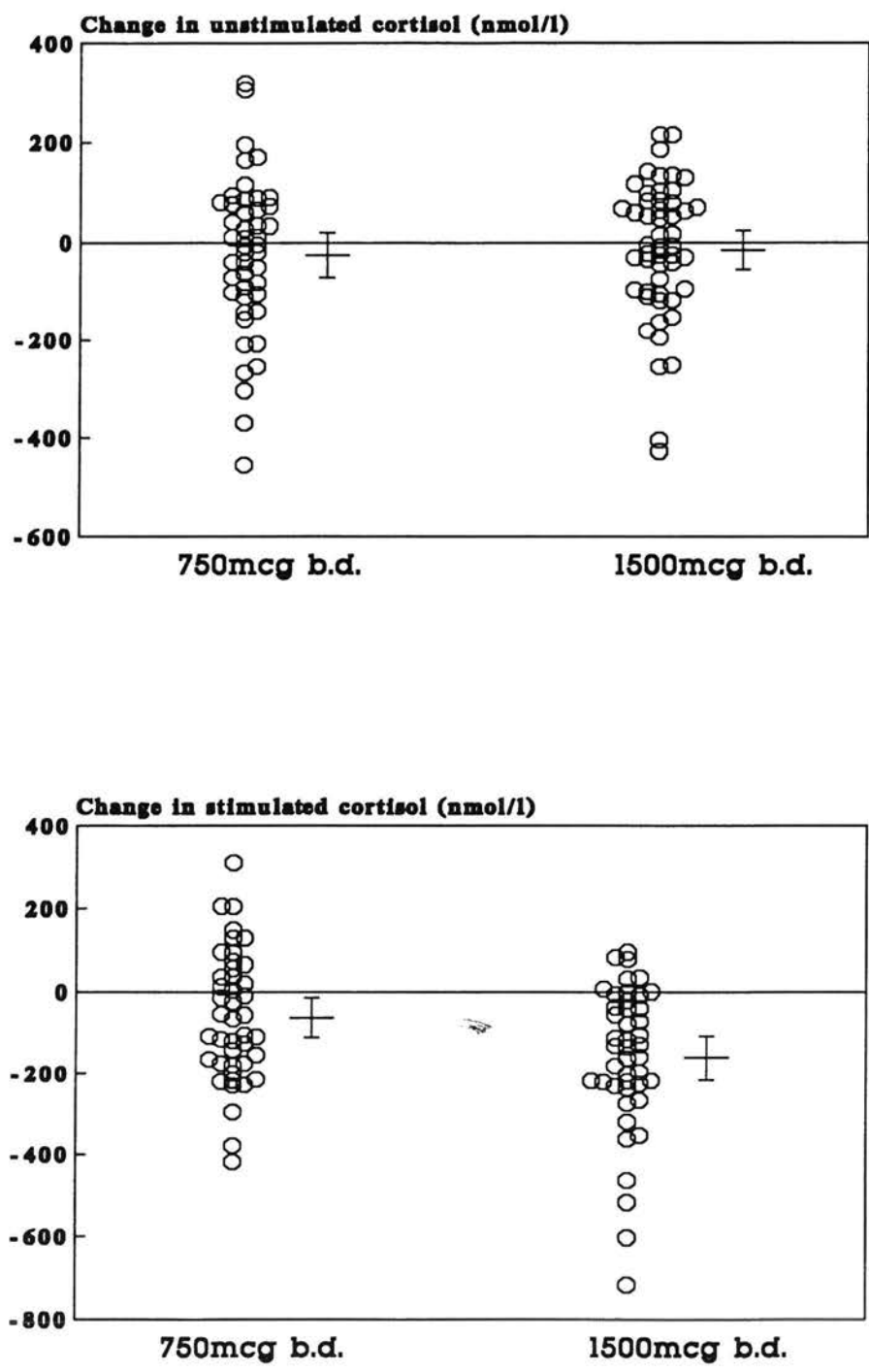


Figure 11.1. The change from baseline values of both unstimulated, and post tetracosactrin serum cortisol levels for the two BDP dose groups, after the first three weeks treatment. Error bars show the mean change and 95% confidence limits for the mean.

At baseline one patient in the 750 mcg b.d. group had an increment in serum cortisol post tetracosactrin of less than 200 nmol/l, and 2 patients in the 1500 mcg b.d. group had post tetracosactrin serum cortisol levels less than 550 nmol/l. However when 'failure' was assessed on the results of both tests, no patient failed both test at baseline.

After inhaled beclomethasone for three weeks the absolute level of serum cortisol post tetracosactrin was above 550nmol/l in all of the patients in the lower dose group, but was below this level in 7 of the 44 patients receiving 1500mcg b.d. (chi squared=7.26, DF=1, p=0.007). The increment 'test' was failed by one patient in the 750 mcg b.d. dose group, and by 5 in the higher dose group (chi squared=2.67, DF=1, ns). However when the results of both tests were combined no patient in the 750 mcg b.d. group failed, and only one of the 44 patients receiving 1500mcg b.d..

In the 28 patients who received inhaled beclomethasone alone for the final treatment phase, there was no significant difference between the dose groups for the number of patients failing the tests of HPA function. The number of patients failing each 'test' were - post tetracosactrin cortisol; 750mcg b.d. group 1/14, 1500mcg b.d. group 4/14 (chi squared=2.19,ns): - cortisol increment post tetracosactrin; 750mcg b.d. group 2/14, 1500mcg b.d. group 2/14: both tests combined; 750mcg b.d. group 1/14, 1500mcg b.d. group 2/14.

### *c. The effect of oral prednisolone.*

Three weeks treatment with oral prednisolone 40 mg per day in addition to inhaled beclomethasone, produced a significant fall in all three parameters of HPA axis function measured (table 11.3.).

The number of patients 'failing' each of the tests of HPA axis function increased after the addition of oral prednisolone to the treatment regime. In the patients receiving inhaled beclomethasone at a dose of 750mcg b.d., 20 of the 23 patients had a post

tetracosactrin serum cortisol of less than 550 nmol/l, in twelve the increment was less than the normal 200nmol/l, and when both tests were combined 11 patients failed this assessment of HPA axis function.

Table 11.3. The mean (95% CI) values for the measures of HPA axis function after three weeks treatment with BDP, and a further three weeks combined treatment with oral prednisolone and BDP, in those patients treated with oral prednisolone during the final treatment phase. Presented for the two BDP dose groups separately.

	BDP alone	BDP+Pred
Unstimulated cortisol.		
750mcg b.d.(n=26)	386 (324-447)	208 (136-280)
	<i>( mean difference -178 (-100 to -256), p &lt; 0.001)</i>	
1500mcg b.d.(n=32)	320 (260-380)	165 (113-216)
	<i>( mean difference -155 (-80 to -231), p &lt; 0.0001)</i>	
Stimulated cortisol.		
750mcg b.d.(n=23)	820 (763-877)	403 (307-498)
	<i>( mean difference -418 (-332 to -504), p &lt; 0.0001)</i>	
1500mcg b.d.(n=29)	705 (635-775)	431 (336-526)
	<i>( mean difference -274 (-182 to -366), p &lt; 0.0001)</i>	
Cortisol increment.		
750mcg b.d.(n=23)	425 (380-469)	221 (179-263)
	<i>( mean difference -204 (-151 to -256), p &lt; 0.0001)</i>	
1500mcg b.d.(n=29)	393 (340-447)	279 (225-333)
	<i>( mean difference -115 (-58 to -173, p &lt; 0.001)</i>	

For the 29 patients receiving 1500mcg b.d. 22 had post tetracosactrin serum cortisol levels of less than 550 nmol/l, and 11 had an increment of less than 200 nmol/l. When the results of both tests were combined 11 of the 29 patients failed the tests of HPA axis function.

To try to determine the relative effect of oral prednisolone and inhaled beclomethasone on HPA axis function, the change between baseline and post treatment stimulated cortisol levels was compared in the patients receiving oral prednisolone and inhaled beclomethasone for the final treatment phase. The mean change (95% CI) in the 23 patients in the low BDP dose group after inhaled beclomethasone alone for three weeks was -43 (-114 to 28) nmol/l, and after the addition of oral prednisolone to the regime was -465 (-557 to -372) nmol/l. In the higher dose group the corresponding figures were, after BDP alone -118 (-167 to -70) nmol/l, and after both BDP and oral prednisolone -418 (-340 to -495) nmol/l.

Hence oral prednisolone 40 mg per day for three weeks in combination with inhaled beclomethasone appears to cause approximately ten times the suppression of the HPA axis as three weeks treatment with inhaled beclomethasone 750 mcg b.d. alone, and four times that caused by 1500 mcg b.d. alone.



### 11.2.2. Local side effects.

#### *a. Oro-pharyngeal candidiasis.*

For this analysis scores from the five point scale used (page 50) were combined to separate patients into those with visible oro-pharyngeal candidiasis (scores 3 and 4), and those with no visible candidiasis (scores 0 to 2).

After three weeks treatment with inhaled beclomethasone one patient (2%) receiving 750mcg b.d. BDP had evidence of oral candidiasis, compared to 5 (9.8%) in the higher dose group. This difference was not statistically significant (chi squared = 1.35, ns). Therefore both doses were combined to assess the effect of inhaled BDP on the incidence of oral candida. After placebo no patients had evidence of candidiasis, whereas 6 had visible candidiasis after inhaled BDP (McNemar test  $p < 0.05$ ).

Of the patients receiving both inhaled beclomethasone and oral prednisolone for the final treatment phase, 24% had visible oral candida, compared to 3% of the patients continuing on inhaled beclomethasone alone (chi squared = 5.4,  $p < 0.04$ ). Of the 15 patients with oro-pharyngeal candidiasis taking both oral prednisolone and inhaled beclomethasone during the final treatment, only 2 had evidence of this problem after three weeks treatment with inhaled beclomethasone alone (McNemar test  $p < 0.003$ ).

#### *b. Dysphonia.*

After three weeks treatment with inhaled beclomethasone only 2 patients, in the lower inhaled beclomethasone dose group complained of severe hoarseness of the voice. The distribution of dysphonia scores is shown in table 11.4.. There was no significant difference in the distribution of scores between the two inhaled beclomethasone dose groups after three weeks of active treatment (Mann Whitney U test  $Z = -0.13$ ,  $n=98$ , ns), and within each dose

group no detectable difference in scores between placebo therapy and inhaled beclomethasone ( 750mcg b.d. group;  $Z = -1.33$ ,  $n=47$ ,ns: 1500mcg b.d. group;  $Z = -0.6$ ,  $n=54$ ,ns).

Table 11.4. Distribution of dysphonia scores after placebo and inhaled beclomethasone in the two BDP dose groups, as percentage of each dose group.

BDP dose	Dysphonia scores							
	Placebo				BDP			
	0	1	2	3	0	1	2	3
750 mcg b.d.	85	15	0	0	85	7	4	4
1500 mcg b.d.	88	8	4	0	78	22	0	0

There was no detectable difference in the distribution of dysphonia scores after the final treatment phase between the patients continuing on inhaled beclomethasone alone, and those receiving both oral prednisolone and inhaled beclomethasone as the final treatment ( Mann Whitney U test  $Z = -0.13$ ,  $n=93$ , ns). The distributions are tabulated in table 11.5..

Table 11.5. Distribution of dysphonia scores after the final treatment phase in the two treatment groups, as percentage of each treatment group.

Treatment group.		
Dysphonia scores	BDP alone	BDP + Pred
0	81	80
1	16	15
2	0	3
3	3	2

### 11.3. DISCUSSION.

It is well recognised that inhaled corticosteroids are much safer than oral corticosteroids, and in asthma equivalent therapeutic efficiency can be achieved with much less evidence of systemic side effects(34). However at higher doses both the systemic and local side effects may be significant and limit the usefulness of such therapy. This part of the study aimed to address this question, and the results show no significant adrenal suppression with the lower dose of inhaled beclomethasone used, and a very low frequency of local side effects with either dose. Inhaled beclomethasone at a dose of 1500mcg b.d. did produce detectable and probably significant adrenal suppression, but this was still less than that seen after oral prednisolone.

Systemic side effects described after treatment with inhaled beclomethasone include suppression of the HPA axis(235,236), changes in calcium and phosphate metabolism (221,222,237) purpura and reduced skin thickness(238), and increases in the levels of cholesterol and insulin in serum(239). In addition inhaled corticosteroid therapy has been implicated in the development of posterior subcapsular cataracts in the eye(240). Local side effects are oro-pharyngeal candidiasis, and dysphonia(241), and rarely patients experience marked cough and bronchospasm after inhalation of beclomethasone, the cause of which is not clear(242).

The results of this study do show adrenal suppression with both doses of inhaled beclomethasone when judged by the change in mean values. However the degree of suppression after three weeks treatment was not great. For unstimulated cortisol the mean values fell by 6.6% in the 750mcg b.d. group and 4.6% in the 1500mcg b.d. group. For the increment in serum cortisol following tetracosactrin the decrease was 6.8% and 27% respectively, and for urinary free cortisol 20% and 40%. In previous studies in normal volunteers treatment with 2000 micrograms per day inhaled beclomethasone depressed basal cortisol levels by 15%, and 4000 micrograms per day by 50% of pre treatment levels(243). The mean post tetracosactrin cortisol levels for both inhaled beclomethasone dose groups seen in my study were well above the lower cut off for a normal response.

This suggests that the adrenal suppression caused by the treatment regimes used is relatively minor.

However when assessed on an individual basis adrenal suppression appears to be more of a problem, especially with the higher dose of inhaled beclomethasone, on which 15% of patients had a stimulated cortisol level lower than the 'pass' level. This measure is probably the best indicator of adrenal suppression, although many endocrinologists include the cortisol increment in assessing the HPA axis(244). As a negative correlation has been reported between the increment in serum cortisol and the starting level of serum cortisol, an association which was also apparent in this study ( $r=-0.43$ ), patients with high basal cortisol levels may 'fail' if undue weight is given to the increment in cortisol.

When a more classical approach to the definition of adrenal suppression in individuals is followed, that is the use of both measures(245), then only one patient failed the assessment of HPA axis short term reserve. Although clinically high dose inhaled corticosteroid therapy does not appear to cause Addisonian problems, it would probably be wise if patients receiving doses in excess of 1500 micrograms per day of inhaled beclomethasone carried steroid warning cards, and in times of prolonged physiological stress, such as trauma or surgery received additional systemic steroids.

The urinary free cortisol results showed the greatest degree of suppression with the higher dose of inhaled beclomethasone. Although there are problems in ensuring a complete 24 hour collection in outpatients, there would be no reason to suppose that these problems would be different at the three stages of the trial. Hence the comparison within patients of the change with active treatment seems to be valid. As the 24 hour urinary free cortisol measurement reflects adrenal secretion of cortisol over a whole day, it may provide different information to that obtained by tetracosactrin tests, and may indicate that the ability of the adrenals to respond to prolonged stress is impaired(246), and that longer term treatment will result in more pronounced suppression. Unfortunately

because of interference by metabolites of prednisolone in the assay the comparison of suppression of the two doses of inhaled beclomethasone and oral prednisolone was not possible.

Previous studies have usually examined the effects of high dose inhaled corticosteroids on adrenal function in normal volunteers or patients with asthma. Interpretation of the results of such studies is difficult as normals may well react differently to patients, and many of the asthmatic patients studied had been or were taking oral corticosteroids in addition to inhaled corticosteroids. Studies on normal volunteers indicate no HPA axis suppression in doses up to 1000 micrograms per day(247), but adrenal suppression is detectable in normals in doses above 2000 micrograms(244).

In a review of all published studies on patients treated with inhaled beclomethasone only 25 previous studies were identified in which patients were not taking any form of corticosteroid prior to the study(248). Of these only six publications used doses in excess of 1000 micrograms per day(237,249,250,251,252,253). The reviewers suggested that in general studies showed that doses of inhaled beclomethasone up to 1200 micrograms per day have no significant effect on HPA axis function, but in doses above this level adrenal suppression may be detected. The majority of these studies used treatment periods of less than 6 weeks, and did not study the effect of longer term administration of corticosteroids. A recently published study has shown a correlation between the duration of treatment with inhaled corticosteroids and the degree of HPA axis suppression(255). In Smith and Hodson's study patients had been taking inhaled beclomethasone for 6 to 60 months in doses from 500 to 2000 micrograms per day, and although their results may have been influenced by short course of oral corticosteroid taken in the preceding year, they are in broad agreement with the shorter term studies(34). Adrenal suppression was only apparent in patients taking more than 1500 micrograms per day of inhaled beclomethasone.

The patients studied for this thesis had not taken any oral or

inhaled corticosteroids within three months of recruitment, indeed most had taken none at all. Despite this difference in patient characteristics the results are generally similar to the studies quoted above.

Another point of interest was the marked individual variation in the susceptibility to adrenal suppression. This has been described previously(256), and may reflect differences in drug pharmacokinetics, HPA axis sensitivity, variation in drug deposition within the lung, and possible differences in compliance. This individual variability makes broad generalisations about the safety of high dose inhaled corticosteroids very difficult.

The use of a spacing device to deliver the inhaled drug will theoretically have reduced the oral deposition of the drug considerably, and led to less systemic absorption via the gastrointestinal tract, but greater systemic absorption via the lungs. The effect of a spacer will therefore depend upon the relative contribution of each mode of absorption to the systemic levels seen. This may differ for different inhaled corticosteroids, and pharmacokinetic differences may partly explain the conflicting evidence on the effect of spacing devices on HPA axis suppression with high dose inhaled corticosteroids(255,257). The use of spacers in this study may account for the low incidence of adrenal suppression seen in individuals on the higher dose of inhaled beclomethasone.

Although local side effects may not be as serious as adrenal suppression, they nevertheless may prevent patients from taking therapy. Toogood et al have previously shown that the frequency of oropharyngeal candidiasis is increased in patients on inhaled corticosteroids when oral prednisolone is given concomitantly(258). However oral corticosteroid therapy had no influence on the occurrence of dysphonia, a problem which reflects vocal cord dysfunction, probably a local steroid induced vocal cord myopathy(259). The results in my group of patients are in concordance with these earlier observations in asthmatics. In the patients studied however I did not observe a relationship between the occurrence of local side effects and the dose of inhaled



beclomethasone taken. Toogood's group have shown a small dose effect, at least in the dose range 400 to 1600 micrograms per day of inhaled beclomethasone(260). The dose effect was more convincing for oropharyngeal candidiasis, and the patients studied were treated with oral prednisolone in addition to inhaled beclomethasone. The use of spacer devices did reduce the occurrence of local side effects in other studies(242,261). It seems likely that the lack of a detectable dose effect in terms of local side effects in our study is due to the use of spacing devices, and possibly because the doses used are at the plateau range of the dose response relationship. Treatment with oral prednisolone did increase the occurrence of oro-pharyngeal candidiasis, so that it appears that systemic steroids augment the local effect of inhaled corticosteroids.

Another difference between this study and many in the literature is in the definition of candidiasis. Our definition was clinically based, that is visible candida colonies had to be present for definite candidiasis. Other studies have shown that candida may be cultured from the mouth swabs from up to 57% of normal subjects(262). Hence interpretation of culture findings is difficult, and clinically based scoring systems are probably more useful.

There have been few reports of the incidence of oropharyngeal candidiasis in patients treated with high dose inhaled corticosteroids that are comparable to the doses used in our study. Most studies have used up to 800 micrograms per day inhaled beclomethasone. The results in this study show a lower incidence of candidiasis than those quoted by Cayton et al, of 77% at a dose of 800 micrograms per day inhaled beclomethasone, or 45% at 400 micrograms per day(263). The likeliest reason for this is the diagnostic criteria used, the use of spacing devices by our patients and perhaps the shorter duration of treatment.

In summary although systemic side effects from the doses of inhaled beclomethasone used were detectable, only a minority of patients showed significant adrenal suppression, less pronounced with the lower dose of inhaled beclomethasone used. This dose was as effective as the higher dose in improving lung function and



symptoms (see chapter 6), so that 750mcg b.d. inhaled beclomethasone appears to be the best compromise between therapeutic efficiency and side effects.

## ***12. THE EFFECT OF INHALED BECLOMETHASONE ON PERIPHERAL NEUTROPHIL ACTIVATION, SPUTUM CHEMOTACTIC ACTIVITY AND SPUTUM ALBUMIN CONCENTRATION.***

This section of the thesis reports the results of a study on the effect of treatment with inhaled beclomethasone on peripheral neutrophil function and bronchial secretions. In particular

- (a) peripheral neutrophil chemotaxis to a standard chemoattractant,
- (b) peripheral neutrophil extracellular proteolysis ,
- (c) the chemotactic activity of sol phase sputum,
- (d) lung inflammation as reflected by sputum to serum albumin ratios.

## **12.1. METHODS.**

### **12.1.1. Patient selection.**

Samples were collected from a subgroup of 24 patients entered into the main study, who were selected simply because they attended the laboratory for physiological assessments in the morning.

The results reported here are limited to the effects of inhaled therapy alone because of the possible interaction of oral and inhaled drugs, and the small number of patients from whom samples were available after oral prednisolone treatment.

### **12.1.2. Sample collection and processing.**

Samples of blood and sputum were collected at the end of the three week baseline period, on the final day of treatment with placebo and at the end of beclomethasone therapy. Ten ml of venous blood was collected into a lithium heparin tube via a 19G needle. Sputum was collected in a sterile universal container by the patient from rising on the day of assessment until attendance at the laboratory 3-4 hours later.

Neutrophils were isolated from peripheral blood by the method of Jepsen and Skottun(264). Each sample of venous blood was diluted with an equal volume of 0.15 mmol/l sodium chloride solution and carefully layered onto the surface of 2 ml 54% 'Percoll' (density 1.075g/l) (Pharmacia AB, Uppsala, Sweden) in 0.15 mmol/l sodium chloride which had been layered onto 3 ml 78% percoll (density 1.096g/l). The tubes were centrifuged at 200g for 25 minutes at room temperature. The PMN layer ( at the interface of the two solutions ) was collected and the cells (more than 96% PMN) were washed three times in sterile hepes-buffered RPMI 1640 medium (Flow Labs, Rickmansworth, Herts), counted, and resuspended at appropriate numbers.

Sputum samples were centrifuged at 50,000g for 90 minutes, the sol phase removed and stored at -40°C until assayed.

### **12.1.3. Chemotaxis assay.**

#### *a. Peripheral PMN chemotactic activity.*

The chemotactic activity of peripheral blood PMN was measured by a modification of the technique of Falk et al(265), using a multiple blind well assay. The lower chamber of each well was filled with 270ul of  $10^{-8}$  molar FMLP (N-formyl-L-methionyl-L-leucyl-L-phenylalanine) dissolved in RPMI medium. The upper chamber was filled with 380ul of hepes buffered RPMI 1640 containing bovine serum albumin 2mg/ml, and  $1.5 \times 10^6$  PMN. The chambers were separated by two membranes, the upper was a polycarbonate membrane of pore size  $2.0 \times 10^{-6}$ m (Nucleopore Corp, Pleasanton, USA) , the lower was a cellulose acetate membrane of pore size  $0.45 \times 10^{-6}$ m (Millipore, Harrow, Middx). Lower control wells contained medium without FMLP. The chambers were incubated at 37°C for 90 minutes, the Millipore cellulose acetate membranes were collected, fixed in ethanol, stained with haematoxylin, dehydrated, and mounted. Membranes were examined at x400 magnification, the numbers of PMN seen in five random fields was counted, and the average determined. Each assay was performed in triplicate and the mean of the 3 membranes was used as a final result for analysis.

#### *b. Sputum chemotactic activity.*

Sol phase sputum diluted 1 in 5 with RPMI medium was used as the chemoattractant in the lower well of the chemotaxis chamber. Peripheral PMN from healthy control subjects were used as the cell source, and all sputum samples from an individual assayed simultaneously against one subjects cells to reduce variability.

### **12.1.4. Extracellular Degradation of Fibronectin by PMN.**

Extracellular proteolytic activity of isolated PMN was measured as digestion of radiolabelled fibronectin, by the method of Campbell et al(266). Fibronectin purified from human plasma was labelled with  $^{125}\text{I}$  labelled sodium iodide (Amersham International,

Buckingham) by the chloramine-T method. The radiolabelled fibronectin was diluted with a solution of unlabeled fibronectin in 0.05 mol/l carbonate/bicarbonate buffer (pH 9.6) to give 2000 cpm/mcg fibronectin. Fibronectin solution (0.2ml; 30 mcg fibronectin; 60,000 cpm) was dispensed into microtitre plate wells ('NUNC', Gibco, Paisley, Scotland), the plates were dried at 37°C, and the wells were washed three times with phosphate-buffered saline (pH 7.2). Neutrophils ( $3.0 \times 10^5$  cells in 0.2 ml RPMI 1640) from the patients were applied to the microtitre wells and the plates were incubated for 3 hours at 37°C in a humidified atmosphere of 5% carbon dioxide in air. All cell preparations were also assayed for fibronectin digestion in the presence of  $10^{-6}$  molar FMLP. Blank wells consisted of culture medium only. After incubation the fluid from each well was collected and centrifuged and the supernatant was assayed for <sup>125</sup>I with an LKB 'Multigamma' counter as a measure of solubilised fibronectin. Fibronectin digestion by each cell preparation was assayed six times and the mean expressed as mcg fibronectin digested in 3 hours by  $3 \times 10^5$  cells, calculated from the specific activity of the <sup>125</sup>I-labelled fibronectin.

All reagents used for neutrophil studies were endotoxin free (<20 ng/l) as assessed by the Kabivitrum Coatest (Flow Laboratories).

#### **12.1.5. Sputum and serum albumin concentrations.**

Albumin concentrations in serum and sol phase sputum were measured in triplicate using standard radial immunodiffusion techniques with anti-human albumin monospecific antisera prepared by the Immunodiagnostic Research Laboratory, University of Birmingham. The mean of the three measurements was used for the final result for each sample.

## **12.2. ANALYSIS.**

To examine for a possible beclomethasone dose effect the change in PMN chemotaxis after active treatment compared to baseline and placebo was examined in the two dose groups by a Mann Whitney U test. Changes with treatment for chemotaxis, fibronectin digestion and sputum albumin concentration were assessed by a Wilcoxon rank sum test for paired data. For changes in lung function parameters paired Student *t* tests were used. Correlations were assessed using Spearman's rank correlation coefficient.

## **12.3. RESULTS.**

The chemotactic response of the patients peripheral blood neutrophils to a standard chemoattractant (FMLP) was measured at baseline in all 24 patients, but samples were available in only 20 patients after all treatment phases. Of the remaining four patients, one failed to attend subsequent appointments, one could not tolerate pressurised inhalers due to coughing, one developed acute bronchitis with purulent sputum, and the baseline biochemical screen revealed unsuspected abnormal liver function due to metastatic liver disease in a further patient who was withdrawn.

The demographic details, cigarette consumption and baseline lung function of the study group are given in table 12.1. Fourteen of the twenty patients fulfilled the MRC criteria for chronic bronchitis as assessed by the questionnaire . However fifteen of the patients produced regular sputum during the study period as assessed by diary card scores (data not included). Nineteen patients were current or ex- smokers. At the time of the study 10 patients were taking inhaled beta 2 agonists alone, 2 inhaled Ipratropium bromide alone, and 8 were receiving both drugs. No patient was taking an oral theophylline preparation.

Fibronectin digestion by PMN was measured in 14 patients at baseline, but we were unable to repeat these measurements in 4

patients, three of whom were unable to attend the laboratory at the appropriate time, and one who withdrew because of coughing due to the placebo inhalers. Only 8 of 15 patients producing sputum at enrollment were able to provide sputum samples for analysis at follow up, although insufficient sample was available from one further patient to measure sputum albumin concentration.

Before treatment there was no correlation between either peripheral PMN chemotactic response, or extracellular fibronectin digestion by PMN and FEV1, FVC, mean PEF, KCO, cigarette consumption or total peripheral leucocyte count.



Table 12.1. The baseline characteristics of the 20 patients.  
as mean(SEM) unless indicated.

Male (female)	13 (7)
Age (years)	66 (1.2)
Current smokers (number)	6
Ex smokers	13
Cigarette consumption as pack years	43 (8)
FEV1 (litres)	1.07 (0.11)
FEV1 (% predicted)	43 (4)
FVC (litres)	2.53 (0.11)
FVC (% predicted)	80 (3)
KCO (mmol min <sup>-1</sup> kPa <sup>-1</sup> l <sup>-1</sup> )	1.22 (0.08)
KCO (% predicted)	68 (5)
Reversibility in FEV1 to 200mcg Salbutamol	
- absolute change (ml)	148 (28.6)
- as % prebronchodilator	16.7 (3.84)
- as % predicted FEV1	6.0 (1.2)
PD20 (umol)	0.75
as geometric mean (range)	(0.07 - >7.8)
Peripheral WCC (x 10 <sup>9</sup> /l)	5.16 (0.33)

### 12.3.1. Lung function.

In the 20 patients there was no significant change in FEV1, FVC and histamine responsiveness after inhaled beclomethasone. However mean PEF showed a small but statistically significant increase with active treatment in these patients (Table 12.2.).

Table 12.2. Changes in lung function parameters with treatment in the subgroup of 20 patients. [as mean (SEM)].

	Baseline	Placebo	BDP
FEV1(litres)	1.07 (0.10)	1.06 (0.13)	1.06 (0.10)
FVC (litres)	2.53 (0.11)	2.55 (0.14)	2.55 (0.12)
mean PEF (l/min)	223 (18)	225 (19)	233 (20) *
Geometric mean PD20 (umol)	0.75	0.73	0.78

\*  $p < 0.05$  for comparison of inhaled BDP with placebo and baseline by paired Student *t* test.

### 12.3.2. Chemotaxis.

#### *a. Peripheral blood PMN chemotaxis.*

Nine patients received the lower dose of beclomethasone, and 11 the higher dose of 1500mcg b.d.. Table 3 shows the effect of treatment on peripheral PMN chemotaxis in the two dose groups. There was no detectable dose effect seen when the absolute change in PMN chemotaxis from baseline after beclomethasone was compared in the two groups (750mcg b.d. group median (range) change [cells per high power field] -25.2 (-51.1 to 60.4), 1500mcg b.d. group -24.1 (-61.8 to 50.3) Mann Whitney U test  $z$ -value = -0.114;ns). Similarly no dose effect was seen when PMN chemotaxis after placebo and beclomethasone was compared (750mcg b.d. group change [cells p.h.f.] 7.8 (-90.2 to 31.8), 1500mcg b.d. group -20.1 (-62.0 to 58.1);  $z$ -value = -1.10;ns). The results for both doses were therefore combined for the remainder of the analysis.

The chemotactic response of the patients peripheral PMN to a standard chemoattractant showed a significant fall from baseline after active treatment (median [range] cells per high power field; baseline 67.6 [27.6 to 122.1], beclomethasone 48.1 [5.37 to 136.3];

$p < 0.01$ ). The average response on placebo therapy (58.8 [22.7 to 123.1]) was not significantly different from baseline or from that seen on active treatment. The individual values are shown in figure 12.1, separated into the two dose groups.

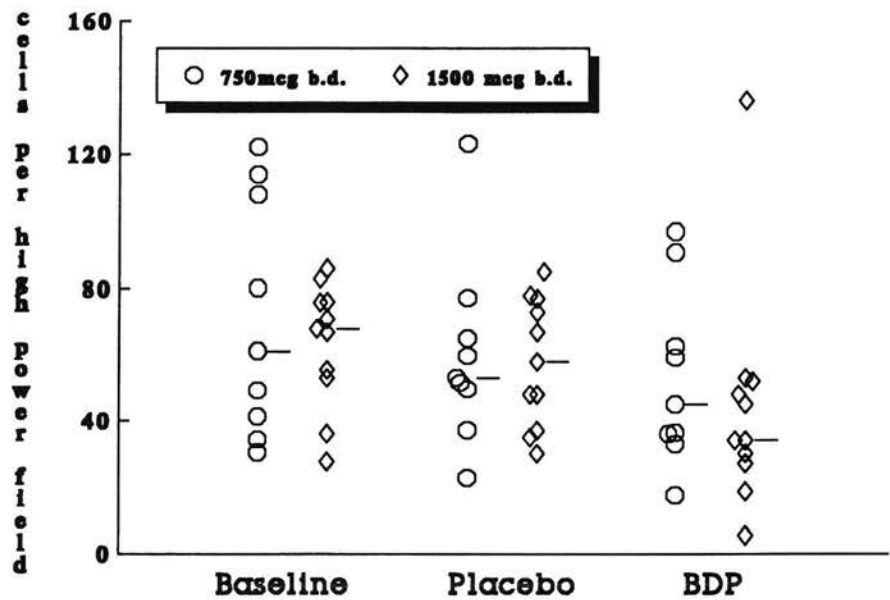


Figure 12.1. Patients peripheral neutrophil chemotactic activity to a standard stimulus, at baseline, after placebo and BDP. Lines indicate medians for each dose group.

*b. Sputum chemotactic activity.*

It was only possible to obtain adequate sputum samples at each phase of the study from 8 patients. The 'chemotactic' activity of sputum sol phase to PMN from a healthy control subject was significantly lower after active treatment than at baseline or following placebo (cells per high power field; beclomethasone 72.2 [46.1 to 102.2]; baseline 88.5 [65.6 to 124.9]  $z = -2.38$ ,  $p < 0.02$ ;

placebo 106.5 [34.6 to 170.6]  $z=-2.24$ ,  $p<0.03$ ). Individual results are shown in figure 12.2., for each BDP dose group.

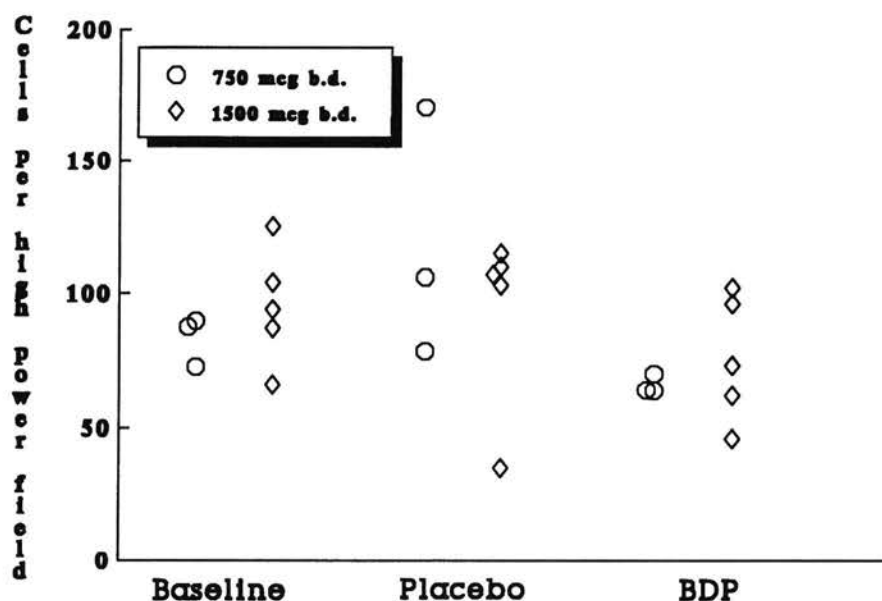


Figure 12.2. Chemotactic activity of 'normal' control neutrophils against patients' sputum, at baseline, after placebo and BDP.

### 12.3.3. Extracellular digestion of fibronectin .

In the 10 patients where it was measured throughout the study spontaneous and FMLP stimulated digestion of  $^{125}\text{I}$ -labelled fibronectin decreased significantly after inhaled beclomethasone compared to baseline and placebo, ( Spontaneous digestion, mcg fibronectin per  $5 \times 10^5$  cells, median [range]; baseline 1.07 [0.4 to 4.23], placebo 1.20 [0.64 to 2.43], beclomethasone 0.50 [0.33 to 1.68];  $p<0.03$  for both comparisons with active treatment: FMLP stimulated digestion; baseline 3.07 [1.09 to 7.76], placebo 1.91 [0.71 to 4.56], beclomethasone 1.12 [0.50

to 2.0];  $p < 0.02$  for both comparisons to active treatment). Individual results for FMLP stimulated fibronectin digestion are shown in figure 12.3..

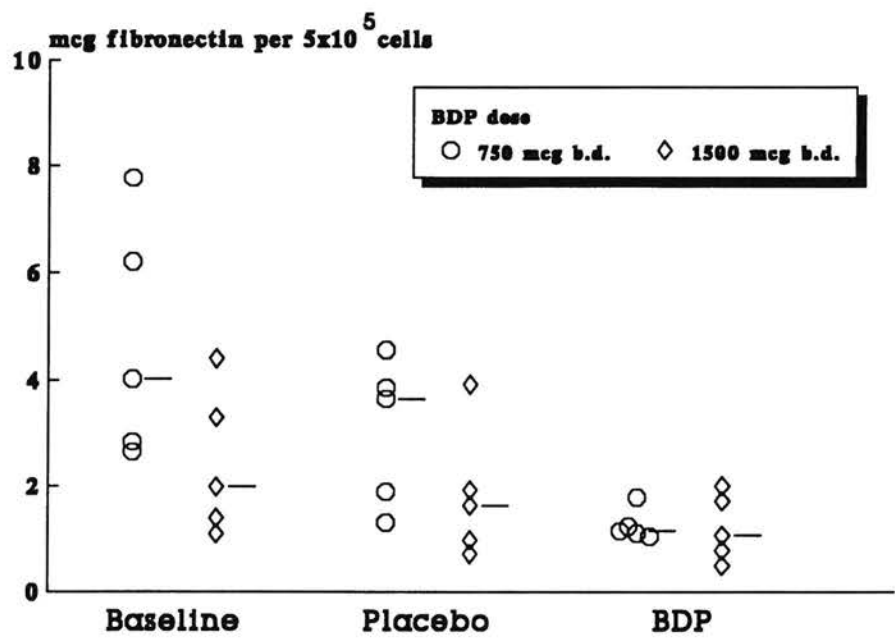


Figure 12.3. FMLP stimulated fibronectin digestion by patients peripheral blood neutrophils, at baseline, after placebo and after BDP. Lines show medians for each dose group.

**12.3.4. Sputum to serum albumin concentrations.**

There was insufficient sputum sol phase in one patient to allow measurement of sputum albumin concentration. In the remaining seven patients the sputum to serum albumin ratio was significantly lower than baseline after inhaled BDP (median[range] sputum/serum ratio x 10<sup>-2</sup>; baseline 0.57 [0.24 to 1.11], BDP 0.29 [0.20 to 0.48];  $p < 0.05$  ). After placebo the sputum/serum ratio ( 0.30 [0.24 to 0.86] x 10<sup>-2</sup> ) was not different to that at baseline or after active treatment.

The changes seen with inhaled corticosteroids were seen in both current and ex smokers, and in patients with and without reduced gas transfer (KCO less than 70% predicted value). There was no relationship between changes in indices of PMN activity or sputum albumin concentration and changes in the lung function parameters in individual patients.

## 12.4. DISCUSSION.

This part of the study has demonstrated that high doses of inhaled corticosteroids *in vivo* reduce the activation of circulating PMN, the chemotactic activity of lung secretions and bronchial inflammation in patients with chronic airflow obstruction.

The results of this section of the thesis must be interpreted with caution for a number of reasons. Firstly the subgroup of patients studied were not selected on a random basis, and hence may not be representative of the patients as a whole. However the timing of patients visits to the laboratory for the physiological assessments was arranged to suit the preferences of the individual patients, and it is therefore unlikely that any bias in terms of peripheral neutrophil function was introduced by this means of selection for the patients for this study. Patients attending morning sessions were selected for the study simply because of the time involved in the isolation of neutrophils, and the setting up of the assays. In addition the physiological characteristics of the 20 patients studied were similar to the 105 patients of the main study, so it is likely the results are applicable to the whole study group.

Because of logistical problems with technical staff and patients, not all 20 patients in whom neutrophil chemotaxis was measured had fibronectin digestion by neutrophils estimated. Indeed only 10 patients had this parameter of PMN function measured at baseline, after placebo and after inhaled beclomethasone. Again although no intentional or obvious bias was introduced, as no overt selection process was applied to pick this subgroup it is possible that they are not representative of the whole study group.

Finally the effect of treatment with inhaled BDP on decreasing sputum production means that the results of both the chemotactic activity of sputum, and the sputum albumin levels reflect the effect of inhaled beclomethasone on a subgroup of patients with more severe bronchial inflammation. It is reasonable to assume that in patients with lesser degrees of bronchial, and bronchiolar inflammation, the anti-inflammatory effect of the



inhaled drug 'switched' off sputum production. Bronchoalveolar lavage would have produced information on all patients, but is an invasive and potentially dangerous procedure. However the effect of inhaled beclomethasone on reducing the numbers of patients producing regular sputum is probably in itself an indication of a potentially beneficial anti-inflammatory effect in the bronchial tree.

Neutrophils are thought to play a central role in the development of chronic airflow obstruction and emphysema(139), and in progression of airflow obstruction in smokers(159). Increased numbers of neutrophils are found in bronchoalveolar lavage fluid in smokers, and in patients with chronic airflow obstruction(147, 149,151). Furthermore PMN from peripheral blood of patients with emphysema and chronic airflow obstruction also show increased chemotaxis and proteolysis(154,156), and superoxide anion generation(155), suggesting a possible mechanism for their proposed role in the pathogenesis of this condition. Inflammation of the bronchial tree also appears to be a cardinal feature of chronic bronchitis and chronic airflow obstruction. This may be seen directly at bronchoscopy(148), or measured indirectly by the increased leakage of albumin into lung secretions(267).

Corticosteroids have been shown to diminish neutrophil activation in a number of experiments. Degranulation of PMN is decreased after incubation with dexamethasone in vitro(156), and the chemotactic response of peripheral neutrophils is reduced after the in vivo administration of dexamethasone(157). Furthermore oral prednisolone reduces bronchial tree inflammation as assessed by albumin leakage(268). It is possible that some of these effects on neutrophil function and bronchial tree inflammation may partially explain the beneficial effect of oral prednisolone on disease progression in chronic airflow obstruction(57,58).

Our study has demonstrated that in the patients completing the study, high doses of inhaled beclomethasone in vivo reduce the activation of peripheral PMN. The results show a wide range of response for the patients prior to therapy in keeping with previous studies(154). There was no change in the chemotactic response at the

end of placebo therapy, but the values at the end of treatment with beclomethasone were significantly reduced compared to baseline values. Comparison of results on treatment with results on placebo therapy shows a reduction after active treatment, but the difference failed to achieve statistical significance, indicating that the overall effect was small and close to the natural inpatient variability. The raw data suggests that the higher dose of beclomethasone is more effective (fig 12.1.), although this was not confirmed statistically.

However studies of another neutrophil function (extracellular proteolysis) were clearer. Spontaneous degradation of fibronectin by patients PMN at baseline showed increased levels similar to those reported previously(154,156). There was no change during placebo therapy but values on treatment with beclomethasone fell by about 50% to levels seen previously in healthy subjects.

On balance the results suggest that inhaled beclomethasone therapy had a significant effect on circulating neutrophil function. However the mechanism remains unknown. It may reflect a decrease in the release of cytokines from the lung during therapy, or a direct effect on the cells of low levels of beclomethasone that may be absorbed into the systemic circulation. If a direct effect on peripheral PMN of systemically absorbed beclomethasone is the cause then such an effect would either be prolonged, or occur at low levels of the drug in the systemic circulation, as all samples were collected at least 12 hours after the last dose of inhaled therapy. Measurement of beclomethasone levels in serum or body fluids is technically difficult, but alternative, easier to measure inhaled steroids are available, and could be used to assess if systemic absorption of the inhaled drug is the cause of the effects seen. Other workers have shown that corticosteroids do reduce the production of inflammatory cytokines by lymphocytes(269), so that an effect on cytokine induced activation of PMN in the lungs is a possible mechanism of action of inhaled beclomethasone.

In addition to the above effects beclomethasone altered the nature of lung secretions. Sputum has been shown to contain factors with predominantly chemotactic activity although a small degree of

chemokinetic activity is also present(270). The present study using healthy control PMN confirmed this chemotactic activity. Again a wide range of values were observed but this did not alter on placebo therapy (Fig 12.2.). However despite the fact that few samples were available for analysis, there was a significant reduction in chemotactic activity after beclomethasone treatment. Again it is uncertain whether this reflects a reduction in the presence of chemotactic factors in the secretions or a direct effect of the steroid that would still be present in lung secretions.

That inflammation in the lung is likely to have been reduced by inhaled beclomethasone is supported by a reduction in sputum/serum albumin ratio. The baseline results show the usual wide range described previously in similar patients(271). Full data was unfortunately only available on 7 patients, since 7 of the 15 patients failed to produce sputum during the active treatment phase and one produced insufficient for this assay. The reduction in secretions in these patients may reflect a general reduction in lung inflammation or the release of secretagogues. Recent data has shown that neutrophil proteinases (elastase and cathepsin G) are exceptionally potent secretagogues(272). Hence a reduction in neutrophil recruitment and subsequent degranulation may have influenced secretion production. Whatever the mechanism the results suggest a reduction in lung inflammation may have occurred.

Overall the results of this part of the thesis suggest that inhaled beclomethasone treatment may alter several factors implicated in the pathogenesis of destructive lung disease in a beneficial direction. It is possible that these effects are additive and if increased neutrophil recruitment and activation are responsible for disease progression inhaled corticosteroid therapy may modify this process advantageously. Such changes may underlie the effect of inhaled beclomethasone on disease progression outlined in the following chapter.

### ***13. OBSERVATIONS ON DECLINE IN FEV1 IN SEVERE CHRONIC AIRFLOW OBSTRUCTION. RELATIONSHIP TO SHORT TERM STEROID RESPONSE AND TREATMENT WITH INHALED CORTICOSTEROIDS.***

#### **13.1. INTRODUCTION.**

Chronic airflow obstruction is a slowly but relentlessly progressive disease. The prognosis appears to be related in part to the underlying cause of the airflow obstruction. The outcome of the disease appears better in patients with asthma than in those in which the airflow obstruction is primarily due to cigarette smoking, when it is often associated with emphysema(36). The disease in non asthmatic patients appears to be more aggressive, and in both clinical and population based studies the prognosis has been shown to be related to the initial degree of airflow obstruction(273,274,275). Other variables appear to influence survival independently of the degree of airflow obstruction such as carbon monoxide gas transfer(274,276,277,278), age(181), cigarette consumption(279), and bronchial hyperresponsiveness(108). Greater reversibility of the airflow obstruction is, in some studies, a good prognostic feature(108,180,277) but not invariably so(280,281).

Patients with chronic airflow obstruction also show a more rapid decline in FEV1 than that expected by age alone. Reported values for the average rate of decline in FEV1 vary from 80 to 85ml per year(108,282,283) to only 34ml per year, not dissimilar to the normal deterioration with age(284). Most authors report rates of decline of between 50 to 60ml per year in established mild disease, but with a wide individual variation(180,276,277,285). It appears that patients with the mildest and most severe impairment in airflow obstruction show the lowest rates of decline in FEV1(181). The increased mortality of the condition is related to this accelerated decline in FEV1(286), although in patients with more severe disease the lower rate of decline in FEV1 probably explains the 'survivor' effect noted by some authors(285,286).

Despite the variety of therapeutic agents available to treat

patients with this disease, only long term oxygen therapy has been shown to affect the outcome in a subgroup of severely affected patients(55,56). Recently two uncontrolled retrospective analyses from Dutch workers have suggested that moderate doses of oral prednisolone may both reduce mortality and slow down the loss of FEV1 in non atopic patients with chronic airflow obstruction(57,58). Their patients were not selected by a short term trial of steroids, as suggested by many(40,41). Indeed the long term significance of a response in such short term trials has never been investigated. It is assumed that responders to corticosteroids in such trials will benefit over the long term by continued treatment with such drugs, and conversely that non responders to short term treatment with corticosteroids will not benefit. There is little if any evidence to support either assumption.

### **13.2. AIM.**

The aim of this part of the thesis was to describe the change in lung function in a cohort of patients who completed a short term steroid trial between 1983 to 1985 and relate decline in FEV1 to various factors previously shown to influence rate of decline in FEV1. The results of this short term 'steroid trial' study have been reported previously(95).

Specifically decline in FEV1 has been related to

- atopy,
- reversibility of airflow obstruction,
- smoking,
- bronchial hyperresponsiveness,
- starting level of lung function,
- the response to treatment during the original trial,
- and to treatment with inhaled corticosteroids during the period of observation.

### **13.3. METHODS.**

#### **13.3.1. Patients.**

The original trial recruited patients over the period 1983-1985. One hundred and twenty one patients with adult onset chronic airflow obstruction completed the original trial. All had an FEV1 less than 70% predicted and symptoms for at least five years. None had a history of chronic childhood respiratory illness, or showed variability in symptoms except in association with infection. Patients with a clinical diagnosis of asthma, or a history of acute attacks of wheezing or breathlessness, and those who gave a history of sudden deterioration following specific allergen exposure were excluded. The presence of airflow reversibility to a bronchodilator was not deliberately used as an exclusion criteria. Full details of the trial are given in Appendix VI.

#### **13.3.2. Design.**

The original 'steroid trial' was a randomised, double blind placebo controlled crossover trial comparing 14 days therapy with oral prednisolone 40mg o.d. to inhaled beclomethasone dipropionate 500 mcg t.d.s.. (Fourteen patients did not receive the placebo phase of this trial).

Follow up assessments were carried out approximately 12 and 48 months after the last patient had completed the trial (figure 13.1).



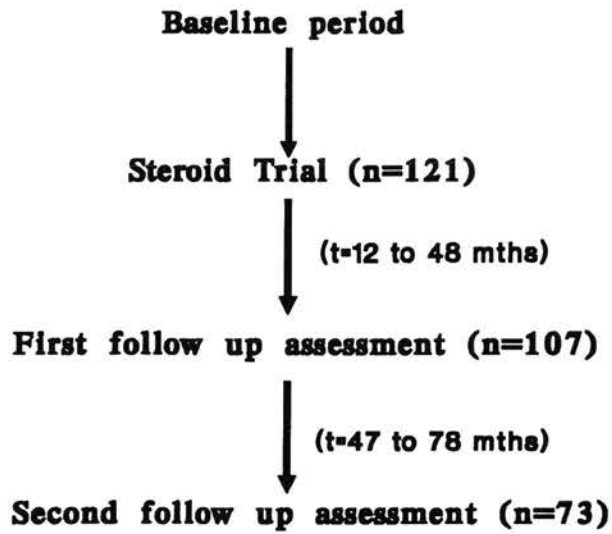


Figure 13.1. Schematic representation of the design of the study.

### 13.3.3. Lung function measurements.

FEV1 reversibility to salbutamol was determined during the run-in phase of the original trial. 200mcg and 10mg of salbutamol were administered sequentially, and the response determined 20 minutes after each dose. The smaller dose was given by a metered dose inhaler, the larger by nebulisation to dryness with an Inspiron mini-neb nebuliser. At the follow up assessments FEV1 reversibility was measured 20 minutes after the administration of 200mcg salbutamol from a metered dose inhaler via a volumatic spacing device. FEV1 reversibility is expressed as a percentage of the predicted FEV1 in view of the independence of this index from the starting level of FEV1(160),



ie reversibility

$$= \frac{\text{post salbutamol FEV1} - \text{pre salbutamol FEV1}}{\text{predicted FEV1}} \times 100$$

Bronchial responsiveness to inhaled histamine (PC20) was measured by the method of Cockcroft et al(161) if the FEV1 was above 0.6 litres during the run-in phase of the original trial, or greater than 0.75 litres at the follow up visits.

At both follow-up assessments patients were asked to abstain from inhaled bronchodilators for 4 hours and oral bronchodilators for 12 hours before assessment. FEV1 and FVC were measured in a sitting position on a dry wedge spirometer (Vitalograph). The best of at least three attempts, with the top two readings within the lower of 10% or 100ml was used for further analysis.

#### **13.3.4. Other baseline tests.**

Serum IgE levels were measured in 97 patients by a PRIST technique. Skin prick tests were performed with house dust, *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, cat fur and a control solution in 98 patients. A positive result was defined as a weal 2mm greater than control in two or more tests.

Smoking status was determined by the replies to a modified MRC respiratory questionnaire. Declared non smoking was confirmed by measurement of the serum thiocyanate level, and/or measurement of the concentration of carbon monoxide in the expired breath using a portable analyser (Morgan Eco-check EC50).

Patients completed a modified MRC respiratory questionnaire, at baseline prior to the original trial, and at each follow up visit. This included questions relating to treatment since the original trial. Answers to these were validated by cross checking with the patients clinical notes.

### **13.3.5. Treatment during the observation period.**

During the period of follow-up the referring physicians were advised to prescribe inhaled beclomethasone at a dose of 750 mcg b.d., in addition to oral and inhaled bronchodilator treatments, irrespective of response to corticosteroids during the acute trial. The drug was not stopped for lack of response or any other systematic reason during the follow-up period. At the first follow up assessment 50 patients were either not taking inhaled beclomethasone at the time of the assessment or had taken it for less than 25% of the follow up period. All these patients were prescribed inhaled beclomethasone at a dose of 750 mcg b.d. at that time.

## **13.4. ANALYSIS.**

### **13.4.1. Definition of steroid response in original trial.**

Response to treatment in the original trial was assessed on the results of FEV1 and FVC measurements on the last day of each treatment phase, or on changes in daily mean peak expiratory flow (PEF) over the final seven days of each treatment, measured five times daily at home. An improvement of at least 20% in any one measurement was classed as a full response to the treatment, and patients not fulfilling these predetermined criteria were considered non responders to corticosteroid treatment. For the purposes of this analysis response refers to a response as defined to either oral prednisolone or inhaled beclomethasone or both.

### **13.4.2. Calculation of decline in FEV1.**

Decline in FEV1 was calculated from the values recorded at the appropriate follow up study, and the initial FEV1. Because of the difficulty in deciding which of the six FEV1 values recorded during the original trial should be used for the starting FEV1, the decline in FEV1 was expressed in three ways.

The primary analyses were performed on the decline calculated from the follow-up value and that recorded at the end of the inhaled beclomethasone treatment phase of the original trial (FEV1 decline).

$$\text{ie; FEV1 decline} = \frac{\text{post BDP FEV1} - \text{follow up FEV1}}{\text{period of follow up (years)}}$$

In addition the decline in FEV1 was calculated by determining the mean FEV1 over the six pre and post treatment values in the original trial, subtracting that recorded at the follow up assessments and dividing by the period of follow up (mean FEV1 decline).

$$\text{ie; mean FEV1 decline} = \frac{\text{mean FEV1} - \text{Follow up FEV1}}{\text{period of follow up (years)}}$$

Finally the decline in post salbutamol FEV1 was calculated by using the post salbutamol value recorded during the run-in phase of the original trial, and that recorded after bronchodilator at the follow up assessments (postbd FEV1 decline).

$$\text{ie; postbd FEV1 decline} = \frac{\text{baseline post salbutamol FEV1} - \text{f up post salbutamol FEV1}}{\text{period of follow up (years)}}$$

A height correction was not used as suggested by others as in this group of patients no correlation between decline in FEV1 and height, height squared or the cube of standing height was seen.

### **13.4.3. Statistical analysis.**

Values for bronchial hyperresponsiveness were logarithmically transformed before analysis. Changes in bronchial hyperresponsiveness are expressed in terms of doubling doses of inhaled histamine. Statistical analysis was by unpaired *t* test for all

normally distributed data or by chi-squared test for categorical data for comparisons between defined groups. Serum IgE levels were logarithmically transformed before analysis.

Pearson correlation coefficients were determined and stepwise multiple regression performed on all the patients with complete data. Variables were rejected if the residual variance of the regression did not change significantly ( $p < 0.05$ ) after addition of the variable, assessed by an F-test.

## 13.5. RESULTS.

### 13.5.1. Analysis of data from first follow up assessment.

The baseline characteristics of the original 121 patients are given in table 13.1.. One hundred and seven of the original 121 patients were assessed at the first follow-up. Of the 14 patients not seen, 7 had died and 7 refused to attend the laboratory or had moved from the area.

Table 13.1. Characteristics of the 121 patients enrolled in the original trial ( as mean (95 % CI) unless indicated).

Number(female)	121 (27)
Age (years)	62.4 (60.8 to 64.1)
FEV1 post BDP (litres)	1.15 (1.06 to 1.24)
FEV1 post BDP (% predicted)	42.7 (39.5 to 46.0)
Mean FEV1 (litres)	1.14 (1.05 to 1.22)
Postbd FEV1 (litres)	1.39 (1.28 to 1.49)
Airflow reversibility to 200mcg salbutamol as % predicted FEV1	7.3 (6.2 to 8.5)
Serum IgE (ku/l) as geometric mean (range)	71 (3-4500)
Number with positive skin tests	56/98
Smoking status (number)	
Current smokers	48
Ex smokers	60
Life long non smokers	13
Cigarette consumption (pack years)	38.5 (33.6 to 43.4)

FEV1 post BDP- FEV1 recorded after two weeks treatment with inhaled beclomethasone during original trial.

Mean FEV1- mean of all FEV1 values recorded both pre and post treatment in original trial.

Postbd FEV1- FEV1 recorded after 10mg salbutamol during run-in phase of original trial.

The period of follow-up ranged from 12 to 44 (mean 26) months. The mean (SEM) FEV1 at the time of this assessment was 0.97 (0.04) litres, or 36.7 (1.5) as a percentage of the predicted value.

The mean (95% CI) values for the three methods of calculating decline in FEV1 over this short period were,

FEV1 decline- 78 (54 to 103) ml/yr,  
mean FEV1 decline- 82 (57 to 106) ml/yr,  
postbd FEV1 decline- 132 (100 to 165) ml/yr.

At the time of first follow-up 71% of the patients were taking regular inhaled bronchodilators, either beta 2 agonists and/or ipratropium bromide, and 20% were taking oral theophylline in addition. The remaining patients were taking inhaled bronchodilators on a prn basis. Only 22% of the patients had taken inhaled corticosteroids for over 80% of the first follow-up period. At the time of this assessment 50 patients either were not taking inhaled BDP or had only started taking the drug in the 8 weeks prior to the assessment.

The differences between two groups of patients, created according to the rate of FEV1 decline over the follow up period was analysed (table 13.2.). One group was defined as showing an improvement or a decline in FEV1 less than the median decline in FEV1 (slow decliners), the other group showed a decline in FEV1 greater than the median (rapid decliners).

The only significant differences between these groups was the higher starting FEV1 (when expressed as a percentage of the predicted value) in the rapid decliners, and the longer percentage of the follow up period for which BDP was prescribed in the slow decliners.

Correlation showed statistically significant associations between FEV1 decline and the starting level of FEV1, the percentage of the follow up time for which BDP had been prescribed, and the carbon monoxide gas transfer (KCO). Patients with a lower FEV1 at

Table 13.2. Characteristics of the 'slow' and 'rapid' decline groups defined, at time of the first follow up in the 107 patients assessed (as mean and 95% CI for mean unless indicated).

	Slow decliners	Rapid decliners	
Number (female)	55 (15)	52 (11)	
Age (years)	62 (59 to 64)	63 (60 to 65)	
FEV1 post BDP (litres)	1.02 (0.91 to 1.13)	1.26 (1.12 to 1.40)	*
FEV1 post BDP (%predicted)	37.5 (33.6 to 41.1)	48.3 (42.9 to 53.6)	
FEV1 reversibility to 10mg salbutamol as % predicted FEV1	8.0 (6.1 to 9.9)	7.2 (5.6 to 8.8)	
P <sub>C</sub> 20 mg/ml as geometric mean	0.60	0.96	
Smoking status [as number (%)]			
Current	24 (44)	16 (31)	
Ex smokers	27 (49)	29 (56)	
Never smokers	4 (7)	7 (13)	
Cigarette consumption (pack years)	39 (31 to 47)	38 (30 to 45)	
Serum IgE (ku/l)	73	72	
Number with positive skin tests (%)	23 (42)	27 (52)	
Number (%) of responders to steroids in original trial	21 (38)	23 (44)	
Percentage of follow up BDP prescribed	55 (46 to 64)	41 (32 to 50)	*

\* $p < 0.05$  by unpaired  $t$  test.



the start of the observation period, those prescribed inhaled beclomethasone for more of the follow up period and patients with better preserved gas transfer tended to have a lower decline in FEV1 (table 13.3.). The same correlations were apparent when mean FEV1 decline was examined, but the KCO did not correlate with postbd FEV1 decline.

In a stepwise multiple linear regression analysis with decline in FEV1 as the dependent variable the following variables were used as predictors,

- the appropriate starting FEV1 (in litres),
- reversibility to 10 mg salbutamol (as a percentage of the predicted FEV1),
- age (in years),
- cigarette consumption (as pack years of smoking),
- the percentage of the follow up period for which inhaled beclomethasone was prescribed (BDP treatment time),
- the volume corrected carbon monoxide gas transfer (KCO),
- the response to steroids in the original trial, (0=non responders, 1=responders),
- log<sub>10</sub> serum IgE level,
- the logarithm of the PC20 value.

For FEV1 decline the starting FEV1, KCO, the percentage of the follow up period for which inhaled beclomethasone was prescribed, and response to steroids in the original trial entered the final equation (table 13.4.). For mean FEV1 decline response to steroids did not contribute significantly to the equation, and for postbd FEV1 decline the starting FEV1, KCO, and cigarette consumption entered the final equation. For post bronchodilator FEV1 decline the percentage of the follow up period for which BDP was prescribed just failed to enter the regression equation ( partial  $r = -0.22$ ;  $p=0.062$ ).

Table 13.3. Correlation coefficients of the three measures of decline in FEV1 with baseline variables.

	FEV1 decline (n=77)	Mean FEV1 decline (n=78)	Postbd decline (n=74)
Starting FEV1 (litres) \$	0.37***	0.32**	0.58***
Age (years)	0.14	0.11	-0.11
Cigarette consumption (pack years)	0.10	0.05	-0.08
Post salbutamol FEV1 (litres)	-0.07	-0.06	-
log <sub>10</sub> PC20	0.14	0.15	0.14
Percentage of follow up period BDP prescribed	-0.22*	-0.31**	-0.23*
Log <sub>10</sub> serum IgE	-0.01	-0.08	-0.15
KCO (mmol/min/kPa/l)	-0.27*	-0.34**	-0.14

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$

\$ Starting FEV1, for FEV1 decline = FEV1 post BDP, for mean FEV1 decline = Mean FEV1, for postbd FEV1 decline = Postbd FEV1 (see table 1).

KCO = carbon monoxide gas transfer per unit alveolar volume

Table 13.4. Parameter estimate b, the standard error of b, the partial correlation coefficient and significance for the multiple regression equations.

1. Dependent variable FEV1 decline (litres/yr)				
	b	SE(b)	partial r	p
FEV1 post BDP (l)	0.12	0.023	0.51	<0.0002
KCO (mmol/min/kPa/l)	-0.09	0.025	-0.34	<0.001
BDP treatment time (% follow up time)	-0.10	0.035	-0.32	<0.01
Steroid response	0.06	0.02	-0.26	<0.025
Intercept	0.18	0.06		
r squared = 0.35    residual SD = 0.11				
2. Dependent variable mean FEV1 decline (litres/yr)				
	b	SE (b)	partial r	p
KCO (mmol/min/kPa/l)	-0.10	0.03	-0.41	<0.0003
Mean FEV1 (l)	0.11	0.03	0.44	<0.0002
BDP treatment time (% follow up time)	-0.09	0.03	-0.30	<0.01
r squared = 0.34    residual SD = 0.12				
3. Dependent variable postbd FEV1 decline (l/yr)				
	b	SE (b)	partial r	p
Post salbutamol FEV1 (l)	0.20	0.03	0.67	<0.0002
KCO (mmol/min/kPa/l)	-0.14	0.04	-0.42	<0.0005
Cigarette consumption (p.yrs)	-0.001	-0.0005	-0.30	<0.02
r squared = 0.47    residual SD = 0.14				

BDP treatment time is the percentage of the follow up time for which inhaled beclomethasone was prescribed.

Steroid response entered as 0=non responder, 1=responder.

### **13.5.2. Analysis of data from the second follow up assessment.**

Seventy three patients from the original 121 were assessed at the second follow up. This occurred on average 62 (range 47 to 78) months after completion of the original short term steroid trial. Twenty five patients had died during the intervening period, the remaining 22 could not be traced. Patients who had died during the follow up period were more likely to be male, were older, and had significantly lower FEV1 values, more gas trapping (as judged from the residual volume measurement), and more impairment of gas transfer (table 13.5.).

The decline in FEV1 over this longer period in the 73 surviving patients was (as mean (95% CI) ;

FEV1 decline- 53 (39 to 66) ml/yr,  
mean FEV1 decline- 53 (38 to 69) ml/yr,  
postbd FEV1 decline- 68 (49 to 88) ml/yr.

Pre bronchodilator decline in FEV1 was similar in the 50 steroid non responders from the original trial, and the 23 steroid responders (table 13.6.). Post salbutamol FEV1 decline (postbd FEV1 decline) was significantly higher in the steroid non responders. The two response groups showed very few differences in physiological characteristics at recruitment to the original trial (table 13.6.).

To investigate the association between bronchial hyperresponsiveness and decline in FEV1, patients were classified into three groups on the basis of the results of the measurement of bronchial hyperresponsiveness prior to the original trial. Patients with a PC20 of less than 0.5mg/ml were considered to have severe bronchial hyperresponsiveness, those with a PC20 between 0.5 to 4 mg/ml moderate bronchial hyperresponsiveness, and patients with a PC20 in excess of 4 mg/ml 'normal' bronchial hyperresponsiveness. There was no significant difference between the three groups in any of the three measures of decline in FEV1 (table 13.7.). The correlation between decline in FEV1 and the logarithm of the PC20 was poor,  $r=0.13$ ;ns. However patients with a PC20 less than 0.5 mg/ml had a significantly lower starting FEV1 at the time of the

Table 13.5. Characteristics of patients dying during the observation period, and those alive at the time of the second follow up assessment, (as mean and 95% CI for mean unless indicated).

	Alive	Deceased	
Number (sex)	74 (20)	25 (2)	*
Age (years)	61 (59-63)	66 (63-69)	*
FEV1 post BDP (litres)	1.22 (1.1 to 1.34)	1.04 (0.87 to 1.21)	*
FEV1 post BDP (% predicted)	45.9 (41.4 to 50.4)	38.0 (31.1 to 44.8)	
FEV1 reversibility as %predicted FEV1	7.5 (5.9 to 9.1)	6.7 (4.1 to 9.3)	
TLC (% predicted)	119 (115 to 123)	127 (118 to 135)	
RV (% predicted)	167 (156 to 179)	191 (171 to 211)	*
KCO (% predicted)	84 (77 to 90)	59 (48 to 69)	*
Cigarette consumption (pack years)	37 (30 to 43)	49 (39 to 59)	
Number with positive skin tests (%)	34 (46)	8 (32)	
Responders to steroids [number (%)]	23 (31)	11 (44)	

TLC = total lung capacity, RV = residual volume,  
KCO = carbon monoxide gas transfer coefficient.

\*  $p < 0.05$  for comparison between groups.

Table 13.6. Characteristics and FEV1 decline over the observation period in the two steroid response groups from the original trial (as mean ((% % CI) unless stated).

	Responders	Non Responders	
Number (female)	23 (6)	50 (14)	
FEV1 post BDP (litres)	1.24 (1.05 to 1.44)	1.20 (1.05 to 1.35)	
Fev1 post BDP (% predicted)	48.4 (39.4 to 57.2)	45.2 (39.7 to 50.6)	
FEV1 reversibility as % predicted	8.0 (5.6 to 10.3)	7.4 (5.3 to 9.5)	
KCO (mmol/min/kPa/l)	1.30 (1.12 to 1.48)	1.17 (1.04 to 1.30)	
Cigarette consumption (pack years)	42 (28 to 57)	33 (27 to 41)	
Serum IgE level (ku/l) (geometric mean)	148	51	
Number with positive skin tests	6/20	30/50	*
FEV1 decline (ml/yr)	52 (30 to 73)	53 (36 to 70)	
Mean FEV1 decline (ml/yr)	42 (15 to 68)	59 (39 to 78)	
Postbd FEV1 decline (ml/yr)	40 (17 to 62)	81 (55 to 107)	*

\*  $p < 0.05$  for comparison between groups.

original trial, and decline measures showed a correlation with the level of FEV1. When decline was compared in the PC20 groups adjusting for the difference in the starting level of FEV1 by an analysis of covariance, the patients with more severe bronchial hyperresponsiveness showed a more rapid decline in post salbutamol FEV1 (postbd FEV1 decline), but not in the other two measures of

Table 13.7. Characteristics and decline in FEV1 in the three bronchial responsiveness groups (as mean (95% CI) unless stated).

PC20 group	severe	moderate	'normal'
Number(female)	35 (8)	13 (4)	13 (3)
FEV1 post BDP (litres)	1.09 (0.97-1.21)	1.48 (1.13-1.83)	1.67 * (1.34-2.0)
FEV1 post BDP (% predicted)	40.0 (34.5-45.6)	58.9 (47.0-70.7)	60.3 * (49.1-71.4)
FEV1 reversibility as % pred FEV1	18.3 (6.4-10.2)	7.9 (5.9-9.9)	8.4 (1.0-15.6)
KCO (mmol/min/kPa/l)	1.17 (1.02-1.32)	1.13 (0.84-1.42)	1.47 (1.19-1.74)
Cigarette consumption (pack years)	35 (26 to 44)	36 (15 to 58)	31 (16 to 45)
Serum IgE level (ku/l) (geometric mean)	78	97	52
Number with positive skin tests	21/35	4/11	3/9
FEV1 decline(ml/yr)	52 (32 to 72)	54 (14 to 95)	77 (57 to 96)
Mean FEV1 decline (ml/yr)	53 (36 to 76)	50 (6 to 93)	81 (38 to 124)
Postbd FEV1 decline (ml/yr)	73 (44 to 103)	54 (23 to 85)	93 (15 to 170)

\*  $p < 0.05$  for difference between severe group and moderate and 'normal' groups.



FEV1 decline ( Mean (SEM) adjusted postbd FEV1 decline  
PC20 < 0.5 mg/ml- 93 (12) ml/yr; 0.5 < PC20 < 4 mg/ml- 44 (19);  
PC20 > 4 mg/ml- 52 (19)).

When decline in FEV1 was compared in smoking groups (smoking status at the time of the second follow up) no difference in the measures of decline in FEV1 were seen (table 13.8.). Only ten of the 73 patients had stopped smoking during the observation period, and we did not find a significant difference in FEV1 decline between these patients [mean(95%CI) FEV1 decline 33 (-2.6 (an increase) to 69) ml/yr], and continuing current smokers [56 (36 to 77) ml/yr] or patients who stopped smoking cigarettes prior to the original steroid trial [56 (33 to 79) ml/yr].

In a stepwise multiple regression analysis in the 58 patients with complete data, the decline in FEV1 over the whole of the observation period was entered as the dependent variable and the following predictor variables used;

- age (in years),
- the appropriate starting FEV1 (in litres),
- reversibility to 10 mg salbutamol (as a percentage of the predicted value),
- cigarette consumption (as pack years of smoking),
- the volume corrected carbon monoxide gas transfer (KCO),
- the response to steroids in the original trial,
- log<sub>10</sub> serum IgE level,
- the logarithm of the PC20 value.

For FEV1 decline and mean FEV1 decline only the starting level of FEV1 entered the regression equation. For post salbutamol FEV1 decline (postbd FEV1 decline) in addition to the starting level of FEV1, age, carbon monoxide gas transfer (KCO) and cigarette consumption added significantly to the prediction of the decline in this measure (Table 13.9.).

Table 13.8. Characteristics and decline in FEV1 three smoking groups (as mean (95% CI) unless indicated).

Smoking status	Ex	Current	Never
Number (female)	44 (5)	22 (8)	7 (7) *
FEV1 post BDP (litres)	1.22 (1.06-1.38)	1.16 (0.93-1.39)	1.36 (1.0-1.72)
FEV1 post BDP (% predicted)	42.8 (36.8-48.9)	45.3 (37.5-53.1)	64.3 (53.8-74.9) *
FEV1 reversibility as % pred FEV1	7.1 (5.3-8.8)	8.8 (4.9-12.7)	7.1 (2.2-11.9)
KCO (mmol/min/kPa/l)	1.18 (1.06-1.29)	1.07 (0.91-1.23)	1.88 (1.5-2.28) *
Cigarette consumption (pack years)	38 (30-47)	45 (37-54)	-
Serum IgE level as geom mean (ku/l)	63	90	89
Number with positive skin tests	21/42	9/21	4/7
FEV1 decline (ml/yr)	55 (36-74)	49 (28-76)	49 (-7 -106)
Mean FEV1 decline (ml/yr)	59 (37-80)	48 (24-72)	38 (-34 -110)
Postbd FEV1 decline (ml/yr)	68 (41-95)	81 (44-117)	34 (2-67)

For abbreviations see table 1, and text.

\*  $p < 0.05$  for comparisons between never smokers, and both current and ex smokers.

Table 13.9. Parameter estimate b, the standard error of b, the partial correlation coefficient and significance for the multiple regression equations for measures of FEV1 decline over the whole observation period.

1. Dependent variable FEV1 decline. (litres/yr)				
	b	SE(b)	partial r	p
FEV1 post BDP	0.44	0.13	0.40	<0.002
Intercept	-0.002	0.018		
r squared = 0.16		residual SD = 0.05		
2. Dependent variable mean FEV1 decline (litres/yr)				
	b	SE(b)	partial r	p
Mean FEV1	0.06	0.02	0.4	<0.002
Intercept	-0.68	0.50		
r squared = 0.16		residual SD = 0.06		
3. Dependent variable postbd FEV1 decline (l/yr)				
	b	SE(b)	partial r	p
Post salbutamol				
FEV1	0.09	0.01	0.66	<0.0001
KCO				
(mmol/min/kPa/l)	-0.08	0.02	-0.52	<0.0002
Age (years)	-0.003	0.001	-0.36	<0.01
Cigarette consumption				
(pack years)	-0.0008	0.0003	-0.32	<0.02
Intercept	0.22	0.08		
r squared = 0.58		residual SD = 0.06		

Thirty two of the fifty patients who were prescribed regular inhaled beclomethasone at the time of the first follow up assessment were reassessed on this occasion. They were similar in most respects to the other patients in terms of physiological characteristics at the time of the original steroid trial. However this group had significantly more steroid non responders than the 39 patients taking inhaled beclomethasone regularly at the time of the first

follow up assessment (table 13.10.).

Table 13.10. Characteristics of the 32 patients prescribed inhaled beclomethasone for the latter part of the observation period only (group I), compared to those prescribed inhaled beclomethasone for the whole of the period (group II), (as mean (95 % CI) unless indicated).

	Group I	Group II
Number (female)	32 (7)	39 (13)
Age (years)	61 (58 to 64)	61 (58 to 64)
FEV1 post BDP (litres)	1.21 (1.02 to 1.39)	1.25 (1.08 to 1.41)
FEV1 post BDP (% predicted)	45.1 (37.8 to 52.3)	47.2 (41.1 to 53.5)
FEV1 reversibility as % predicted FEV1	6.4 (4.7 to 8.1)	8.5 (6.0 to 11.0)
KCO (mmol/min/kPa/l)	1.15 (0.98 to 1.32)	1.23 (1.1 to 1.37)
Cigarette consumption (pack years)	33 (23 to 43)	40 (31 to 49)
Serum IgE level (ku/l) as geometric mean	53	98
Number with positive skin tests (%)	15 (47)	19 (49)
Number of steroid responders in original trial (%)	5 (16)	16 (41) *
FEV1 decline over the first follow up period (ml/yr)	112 (63 to 160)	35 (-8 to 78)

\*  $p < 0.02$  for comparison.

Decline in FEV1 estimated by all three methods is shown for the two groups in table 13.11.. In the 32 patients starting inhaled BDP midway through the study period, all three measures of FEV1 decline fell significantly. In patients prescribed inhaled beclomethasone throughout the study period decline in FEV1 as measured by FEV1 decline and mean FEV1 decline did not change significantly over the two observation periods, although the trend was for a more rapid decline over the second period of observation. Post salbutamol FEV1 decline was significantly less over the second period of observation. For all three measures of decline in FEV1 the rate of decline over the second observation period was not significantly different between the two BDP treatment groups.

Table 13.11. Measures of decline in FEV1 over the first and second period of observation in patients starting BDP midway through the study period (Group I), and those receiving BDP for the two periods of observation (Group II). As mean (95 % CI).

Group I	First period	Second period
FEV1 decline <i>Mean difference</i>	112 (63 to 160) 86 (12 to 160)	25 (-15 to 65) $t=2.36, p<0.03$
Mean FEV1 decline <i>Mean difference</i>	127 (81 to 173) 101 (33 to 171)	25 (-15 to 65) $t=3.0, p<0.006$
Postbd FEV1 decline <i>Mean difference</i>	167 (118 to 216) 154 (85 to 222)	13 (-26 to 53) $t=4.57, p<0.0002$
Group II		
FEV1 decline <i>Mean difference</i>	35 (-8 to 78) 30 (-22 to 82)	65 (44 to 86) $t=1.16, ns$
Mean FEV1 decline <i>Mean difference</i>	31 (-17 to 78) 34 (-18 to 86)	65 (44 to 86) $t=1.33, ns$
Postbd FEV1 decline <i>Mean difference</i>	131 (66 to 195) 93 (20 to 167)	38 (7 to 68) $t=2.58, p<0.01$

Bronchial hyperresponsiveness to inhaled histamine was measured at the time of the original trial, and at the second follow up assessment in 35 patients. There was a small but statistically significant improvement in bronchial hyperresponsiveness of a mean of 0.87 doubling concentrations of histamine (95% CI= 0.18 to 1.56). This was despite a fall in FEV1 from a mean (95% CI) of 1.51 (1.33 to 1.69) to 1.22 (1.06 to 1.38). This was not apparent in the 37 patients who were taking inhaled beclomethasone regularly at the time of the first follow up, and who had  $P_{20}$  values measured. These patients showed a mean improvement over this shorter period of only 0.2 doubling concentrations (95 % CI- -0.47 to 0.9).

### **13.6. DISCUSSION.**

This retrospective observational study has revealed rates of decline in FEV1 over the longer observation period of 50 to 70ml per year depending upon the method used to calculate the decline. This is similar to that reported in the literature for mild disease(180,276, 277,286) but considerably less than the 80 to 85ml per year reported for patients with disease of similar severity(283), or for patients with 'typical COPD' and an initial FEV1 greater than 45% of the predicted value (87 ml per year)(274).

In our study decline in prebronchodilator FEV1 calculated over the whole of the observation period was related to the initial level of the FEV1 alone, with patients with a higher initial FEV1 showing a more rapid decline in FEV1. We found no effect on pre-bronchodilator decline in FEV1 of bronchial hyperresponsiveness, or the short term response to a 'trial of steroids'. In the simple comparative analysis post salbutamol FEV1 decline was higher in those patients unresponsive to a 'trial of steroids', and, when adjusted for the starting level of FEV1, in patients with severe bronchial hyperresponsiveness. However neither of these factors entered the multiple regression equation when this analysis was performed. Smoking status appeared to have no effect on the rate of decline in FEV1 in the comparative analysis, although in the multiple regression analysis cigarette consumption was related to post salbutamol decline in FEV1, calculated over the whole of the observation period.

The results also suggest that treatment with inhaled beclomethasone may have a beneficial effect on the progression of the chronic airflow obstruction. At the time of the first follow up assessment a relationship was detected between the percentage of the follow up time for which inhaled beclomethasone had been prescribed, and decline in FEV1. This effect persisted for both measures of prebronchodilator FEV1 decline when possible confounding factors were taken into account in the multiple regression analysis. For post salbutamol FEV1 decline the effect of treatment with inhaled beclomethasone on the prediction of this measure of decline in FEV1 just failed to reach statistical



significance. Although this data was uncontrolled the association is certainly interesting.

In addition in the thirty two patients who were prescribed regular inhaled beclomethasone after the initial follow up assessment a dramatic fall in the decline in FEV1 was seen at the second assessment. This was true for all three methods of calculating FEV1 decline, and was not seen in those patients taking BDP throughout the study period, who had a low rate of decline in FEV1 over the initial period of observation, and tended to show a slight acceleration in rate of decline of prebronchodilator FEV1 over the second observation period. Although these patients did not enter a formal controlled trial, the first observation period can effectively be considered as a control period without treatment.

Taken together these pieces of evidence suggest that inhaled beclomethasone has a disease slowing effect. There are a number of potential confounding factors which makes interpretation of these results difficult however. The patients who died during the observation period are likely to have had a rate of decline higher than the average, and the 'loss' of these patients in the analysis may bias the results. The fifteen patients seen at the first follow up assessment who died during the latter half of the observation period showed a more rapid decline in FEV1 during the first observation period than those surviving, although the difference was not statistically significant ( mean (95% CI) deceased 109 (69 to 150), survivors 69 (37 to 101) ml/yr). However patients not taking inhaled BDP at the time of the first follow up assessment who died during the second observation period had a similar rate of decline in FEV1 over the first period of observation as those surviving (mean (95% CI) survivors 112 (64-160) ml/yr, deceased 104 (61-146) ml/yr). Hence the comparison of decline in FEV1 before and after treatment with inhaled beclomethasone is probably free of this potential bias.

Another potential problem in interpreting this data is the relation between the level of FEV1 and decline in FEV1. Over the period of observation the FEV1 will fall and hence the rate of decline in FEV1 will also fall, and appear to be the result of treatment.

However inspection of the actual levels of FEV1 at the time of the first and second observation periods shows no significant change, so that although this is certainly a potential bias over a longer term, the effect on the results seen is negligible.

Whether this results from a slowing of the rate of loss of FEV1, or via a longer term response and improvement in FEV1 followed by the inevitable decline is not clear. The data from the group prescribed BDP throughout would suggest that the latter is the more plausible explanation. Postma et al suggest that oral prednisolone may produce an improvement in FEV1 over 6 months or longer in similar patients(57), and it is likely inhaled corticosteroids will act in a comparable way. Only a prospective study with more frequent estimations of FEV1 will answer this question.

The results of our analysis also question the usefulness of short term 'steroid trials' in the management of this group of patients(40,41). Implicit in the recommendation to assess steroid responsiveness in all patients with symptomatic chronic airflow obstruction is the assumption that unresponsive patients do not benefit from treatment with steroids in the long term. There is no published data to support this assumption.

Of the 32 patients starting regular inhaled BDP at the time of the first assessment 27 were classed as non responders after the initial 'steroid trial'. In this subgroup the FEV1 decline improved from a mean (95%CI) of 102 (52 to 153)ml per year to 29 (-16 to 75)ml per year, a difference which just failed to reach statistical significance but is non<sup>P</sup>the less marked, and suggests a beneficial effect of inhaled beclomethasone on non responders to a short term 'trial of steroids'.

The method of calculation of decline in FEV1 may also lead to problems of interpretation of the data. For instance in the analysis of the first follow up data the multiple regression suggested a detrimental effect of a positive steroid response on subsequent decline in FEV1 (as FEV1 decline). This may be true but is likely to be partly artifactual due to the method of calculation of FEV1

decline adopted. By taking the improved level of FEV1 after 2 weeks treatment with BDP as the starting level, we may bias the calculation of decline in FEV1 because of the association between higher starting FEV1 levels and an increased rate of decline in FEV1. The fact that steroid response did not enter into the prediction equations for mean FEV1 decline and post salbutamol FEV1 decline support this interpretation, and indicate that acute steroid response does not predict subsequent decline in FEV1.

The calculation of rate of decline in FEV1 was performed in a variety of ways. It is difficult to know which of the values of FEV1 recorded during the original trial should be used to calculate the decline in FEV1. We selected the FEV1 measured after the inhaled beclomethasone phase of the original trial as patients were treated with this drug during the follow up period. However using the mean of the FEV1 values from the original trial gives similar results. In addition using the best FEV1 from the original trial, or the run-in pre treatment value does not alter significantly the conclusions of this analysis (data not presented). The relatively high rates of decline in FEV1 from the first follow up assessment reflect the relationship between the period of follow up and decline in FEV1 previously described(283,287). Intuitively however such methodological problems should apply equally to all patients and not introduce bias.

Post salbutamol FEV1 decline was higher than that calculated from prebronchodilator values. The reason for this is not clear. This measure of decline also showed some differences from the other two measures used. It was lower in patients showing an acute response to corticosteroids, and after adjustment for starting level was higher in patients showing more severe bronchial responsiveness to inhaled histamine. It may be that the post salbutamol FEV1 reflects the reversible component of bronchial inflammation on a baseline level of airway narrowing. With time fibrosis may ensue, and both bronchodilators, and bronchoconstrictor agents may be less effective. Hence post bronchodilator FEV1 may fall more quickly than pre bronchodilator FEV1. Only more frequent estimations of FEV1 and reversibility in a prospective study will answer this.

The association between a lower decline in FEV1 in patients with the greatest impairment in FEV1 has been described before(180,279,286). The explanation is probably that patients with severe disease only survive to produce data for an analysis of decline in FEV1 if their individual FEV1 decline is less than that seen in the group as a whole. Death during the follow up period was associated with worse pulmonary function, a fact noted previously(274,280,286).

The Groningen group have published evidence to support the Dutch hypothesis of a pivotal role of bronchial hyperresponsiveness in the development and progression of chronic airflow obstruction(39). In a group of well defined non allergic patients with chronic airflow obstruction they showed an independent effect of bronchial hyperresponsiveness on decline in FEV1(108). We have not been able to confirm this in our heterogeneous patient group. A number of possible explanations exist for this discrepancy, not least the patient selection. The Dutch study included patients with less severe disease ( $FEV1 > 1.2$  litres), and they selected a homogeneous group with respect to the severity of airflow obstruction ( $FEV1/FVC$  between 40-55%). Their patients were also considerably younger than our group, and the most responsive patients showed a mean decline in FEV1 of 127 ml/year. These factors alone may explain the differing conclusions reached.

The association between the degree of airflow obstruction and bronchial hyperresponsiveness in chronic airflow obstruction suggests geometric factors are the primary determinant of response to inhaled histamine. However the small improvement in bronchial hyperresponsiveness seen in the study group over the observation period despite a fall in FEV1, which would be expected to worsen bronchial hyperresponsiveness, suggests that even in these patients with severe chronic airflow obstruction factors outside geometry do influence bronchial hyperresponsiveness. This improvement in PC20 values may reflect prolonged treatment with inhaled corticosteroids.

Our data showed no effect of reversibility of airflow obstruction on decline in FEV1 (in the multiple regression analysis).

There was no suggestion that better reversibility equated with an accelerated decline in FEV1, but neither did our data support the contention that a degree of reversibility is a good prognostic sign. It was surprising that no effect of smoking status on decline in FEV1 was detected, although cigarette consumption did significantly predict post salbutamol FEV1 decline. The number of patients changing smoking habit during the observation period was probably too small to produce a detectable effect, or alternatively the effect of smoking cessation may take longer than the period of observation to become apparent. Another possible explanation may be that the effect of treatment with inhaled beclomethasone outweighs the deleterious effect of smoking. Postma et al have published evidence suggesting this is the case with oral prednisolone(57).

Our original patient group was intended to reflect the population of a general chest clinic. Patients were only recruited if the consultant chest physician thought the diagnosis was not, or was unlikely to be asthma. The diagnosis can be difficult in elderly patients who have smoked heavily, and have severe physiological abnormalities, and the argument in these patients is largely semantic. It is possible that we inadvertently included occult 'asthmatics' in the population studied. However the results of the multiple regression analysis show that reversibility of airflow obstruction, a feature of asthma, was not a predictor of decline in FEV1. Hence it is likely that any bias introduced by their inadvertent inclusions is not significant. The results as they stand can be applied to the general chest clinic population with chronic airflow obstruction.

The Tucson group have suggested that the airflow obstruction is more benign in the patients with 'asthma'(36), in that the rate of decline in FEV1 is nearly normal. It is possible this reflects responsiveness to anti-asthma treatment, although no data has been provided about treatment use in their study group. As treatment with corticosteroids appears to be related to a diagnostic label of asthma(288), it is possible that the difference in decline in lung function between 'asthmatics' and 'typical COPD' patients in Burrows population study is partly explained by treatment.



The data analysed for this part of the thesis were collected in a controlled fashion, but not from a controlled therapeutic trial, and hence must be interpreted with caution. Many confounding factors could influence the results, but we believe the consistency of the results when different methods of calculating FEV1 decline are used does strengthen the conclusions. Bias in the prescription of inhaled beclomethasone may be a confounding factor with the data from the first follow up assessment. However the results of starting the 32 patients on inhaled beclomethasone at this time provides stronger, if uncontrolled, evidence that inhaled corticosteroids can slow down disease progression.

The final answer to question of the role of inhaled corticosteroids in non asthmatic chronic airflow obstruction will require a long term prospective randomised controlled study. One such study is underway with another planned. At the moment physicians in the West Midlands commonly prescribe inhaled corticosteroids to patients who do not have asthma (DC Weir, PS Burge; data presented at the British Thoracic Society summer meeting, Birmingham 1990), so the results of this analysis will at least reassure those who do that their current practice is not without some justification. It would also appear ethical to enter such patients into a long term trial without first performing an acute steroid trial.

#### ***14. DISCUSSION AND CONCLUSIONS.***

The rationale for the main part of this thesis was to determine whether the same short term effect as that seen after treatment with oral prednisolone 40mg per day, could be achieved after treatment with high dose inhaled corticosteroids, without the systemic side effects seen after oral prednisolone. If so high dose inhaled therapy could be substituted for oral prednisolone in 'steroid trials', and subsequent treatment in 'responders'. Two high doses of inhaled beclomethasone were used, and their efficacy compared. In addition in an attempt to determine the mechanism or mechanisms by which corticosteroids produced their beneficial effect, changes in bronchial hyperresponsiveness with treatment were documented, and a subsidiary study on a subgroup of patients measured the effect of inhaled therapy on peripheral neutrophil function. Finally an uncontrolled retrospective study investigated the relevance of short term steroid response, and the effect of inhaled steroid therapy on disease progression in chronic airflow obstruction.

The results showed that inhaled beclomethasone at both doses used was more effective than placebo in producing improvement in physiological measures, and in some subjective parameters. There was no significant difference between the doses used in terms of the primary end points selected, although a greater effect of the higher dose on post bronchodilator FEV1 was seen. In addition the subjective changes seen tended to be more pronounced in the higher, 3000 mcg per day, dose group. Both doses were shown to be as effective as oral prednisolone, both in a 'group' analysis, and a 'categorical analysis'. Tests of adrenal suppression showed, perhaps not surprisingly, that the lower dose of inhaled beclomethasone was the safest therapy, and the data from local oropharyngeal side effects, and global respiratory muscle strength supported 750 mcg b.d. of BDP as the dose of choice, in terms of the balance between efficacy and side effects.

The results of the measurement of bronchial hyperresponsiveness showed no effect of treatment, unless a small subgroup of patients, with more severe bronchial



hyperresponsiveness were analysed separately, and in this subgroup the results may be explained by regression towards the mean. Peripheral neutrophil function, and the inflammatory nature of lung secretions were both reduced by treatment with inhaled beclomethasone, with a trend towards a greater effect of the higher dose used.

Although these results are of interest, perhaps the most interesting data comes from the retrospective study. Before considering this, and the implications of the results of this part of the thesis, I would first like to discuss some of the points already raised in the appropriate chapters which may affect the validity of the results obtained.

Firstly by design the trial was a sequential nature, with the investigator therefore aware of which treatment phase was placebo, which inhaled BDP alone, and which oral prednisolone. It was felt that the results of our previous analysis concerning the time course of action of steroids in chronic airflow obstruction, meant that to perform a double blind cross over study a minimum six week washout period after each treatment period was required to avoid any carry over effects. This would lengthen the study period to over seven months, which we felt was too long. The increased dropout of patients entered outweighed any benefit gained by increasing the scientific purity of the study, for the results of the study would have been less applicable to the general clinic population. In addition as the investigator was blind to the BDP and prednisolone dosage groups, the only part of the trial in which bias could have been introduced was in the comparison of placebo with active treatment. I believe by applying rigid criteria to the tests of lung function, and using validated instruments for assessing subjective change any bias unintentionally introduced has been minimised, and is not significant.

Another controversial area in such studies as this one is the patient selection. This has been discussed fairly extensively in chapter 4. The splitting of the elderly patients studied into asthmatics and non asthmatics is largely a semantic exercise. The

entry criteria excluded patients whom the referring physician believed had asthma on clinical grounds. In the absence of a diagnostic test for asthma, such a criteria is justified. Hence patients in whom the benefits of corticosteroids were proven were excluded, and the population recruited were therefore patients in whom a 'trial of steroids' is recommended. As such the results of the study should be applicable to the many such patients who present to chest physicians.

The subanalyses carried out tend to support my contention that the split into asthma and non asthma in this patient population does not achieve anything. Arguments against the contention that a substantial number of 'missed' asthmatics have been included in the study population are numerous. The patients were elderly, ex or current smokers (except one individual), and had developed symptoms in later life. They had a prevalence of atopy as measured by skin test reactivity similar to normals of the same age. Serum IgE levels appeared to be high, but levels were similar in patients categorised as 'asthmatic' or 'non asthmatic' on the basis of questionnaire answers, and the high levels may simply reflect the cigarette smoking of the group. Reversibility of FEV1 to beta 2 agonists was similar in the 'asthmatic' and 'non asthmatic' patients, and less than 10% showed an improvement in FEV1 of over 15% of the predicted FEV1 following salbutamol. Variability in PEF was similar to that described in the normal population recently(184). Finally the lack of any difference in terms of 'asthmatic' features between responders and non responders to inhaled beclomethasone suggests the majority of patients studied had non asthmatic disease.

Indeed the implicit assumption in many past studies that steroid responders are simply missed asthmatics is not supported by the results of my studies. The discriminant function derived from our initial study did include some features many would associate with asthma. However when the function was applied prospectively to this study population, prediction of response to BDP was no better than by chance, suggesting 'asthmatic' features are not important in determining response in this group of patients. Perhaps the basis for steroid responsiveness in these patients lies in the degree and type of

microscopic emphysema present in each individual, as recently described by Cosio's group(289). Only studies incorporating bronchial wall histology, and more complex, and invasive physiological tests could answer this.

Another possible point of contention is the classification of individual patients into responders and non responders to treatment. On a group analysis the active drugs do have a small, but statistically significant effect on physiological measures when compared to placebo, but the validity of arbitrarily categorising patients into response groups may be questionable. Historically the majority of trials studying oral steroid therapy in chronic airflow obstruction have used this approach, and usually with similar cut off points to those used in this study. I have used three variables to classify treatment response, as our previous study did, and although this undoubtedly increases the response rate to treatment, and explains the higher rate seen in this and our previous study compared to others, it increases the risk of attributing clinical significance to changes which are little more than normal variation. Although the correlation between changes in single physiological and subjective measures was poor, patients classed as physiological responders did show greater and statistically significant changes in most subjective measures, and hence the classification system adopted appears to be reasonable, in that it distinguishes between both objective and subjective response. It would also appear to be a reasonable aim of treatment to optimise physiological function alone, as FEV1 is closely related to death from chronic airflow obstruction.

However when the data is examined more closely the change in each of the three variables after treatment shows a unimodal distribution, and not the bimodal distribution one would expect if responders and non responders to treatment were truly biologically different. This observation, the difficulty in predicting a response to treatment, which implies a heterogeneity of the population with respect to steroid response, and the contention by the Groningen group that steroid effects in patients with chronic airflow obstruction may take up to 9 months to be effective, all cast doubt on the validity

of short term steroid trials to determine steroid responsiveness. The Dutch workers did not determine short term steroid responsiveness prior to their study. Only if a short term steroid response equates with a longer term response, and hence better prognosis, and vice versa, that non responsive patients do not show a longer term response to treatment would the continuation of short term steroid trials be justified.

The data from our retrospective study would support this contention, and suggest that the concept of short term steroid response may be fallacious. Although this data was collected outside a controlled clinical trial, the change in decline in FEV1 in the patients starting treatment half way through the follow up period is strong evidence for a significant treatment effect in all patients, both short term steroid responders and non responders. Indeed the majority of those patients starting treatment at this point in the observation period were short term steroid non responders. It is possible we are seeing a longer term, say 6 to 9 month, steroid response, followed by the expected accelerated decline in lung function, but only a long term prospective study with more frequent measurements of FEV1 to demonstrate the pattern of change in FEV1 will clarify this point. We are currently performing such a study in our centre, and organising a multi-centre study to investigate this point more fully. Another European wide study, under the auspices of the European Respiratory Society, Euroscop, is already underway, and more data on this problem should be forthcoming in the near future from the Groningen group. In the not too distant future the role of inhaled corticosteroid therapy in this patient population should therefore be more clearly defined.

Interestingly the effect of treatment on peripheral neutrophil function in this study, could possibly underlie such a disease retarding effect of inhaled corticosteroids. Further studies will be needed to confirm these findings, and clarify the mode of action of inhaled corticosteroids. Studies need to address whether inhaled corticosteroids reduce local pulmonary production of cytokines, and secretagogues, and indirectly reduce neutrophil activation, or whether the action is by a direct effect on the cells following

absorption of the drug into the systemic circulation. It would be appropriate to use a fluorinated corticosteroid in such a study, as these show less systemic absorption, and can be measured in body fluids.

At the moment inhaled corticosteroids do improve lung function and symptoms over the short term in this group of patients. This 'group' effect, and the data from the retrospective study, strongly suggest the concept of short term steroid trials is redundant, and argue for the more liberal prescription of such treatment to patients with chronic airflow obstruction. A recommendation that appears to be normal practice for a high percentage of UK respiratory physicians already.

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## ***APPENDIX I. BASELINE RESPIRATORY SYMPTOM QUESTIONNAIRE.***

### **Steroid Trial Initial Questionnaire**

Please use the actual wording of each question. Put 1=yes or 2=no, or other codes as indicated in the boxes. When in doubt record as no.

I am going to ask you some questions about your chest, please answer yes or no whenever possible.

#### **COUGH**

1. Do you usually cough first thing in the morning in the winter?
2. Do you usually cough during the day - or at night - in the winter?
3. Do you cough like this on most days for as much as 3 months of the year?

#### **PHLEGM**

4. Do you usually bring up any phlegm from your chest first thing in the morning in the winter?
5. Do you usually bring up any phlegm from your chest during the day - or at night - in the winter?
6. Do you bring your phlegm like this on most for as much as 3 months of the year?

#### **BREATHLESSNESS**

7. At your best are you troubled by shortness of breath when hurrying on level ground or walking up a hill ?

If yes:-

8. At your best do you get short of breath walking with other people of your own age on level ground ?

If yes:-

9. At your best do you have to stop for breath when walking at your own pace on level ground ?

If yes:-

10. At your best are you breathless when washing or dressing ?

11. At your worst are you troubled by shortness of breath when hurrying on level ground or walking up a hill ?

If yes:-

12. At your worst do you get short of breath walking with other people of your own age on level ground ?

If yes:-

13. At your worst do you have to stop for breath when walking at your own pace on level ground ?

If yes:-

14. At your worst are you breathless when washing or dressing ?

#### WHEEZING.

15. Does your chest ever sound wheezing or whistling ?

If yes:-

16. Have you ever had attacks of shortness of breath with wheezing ?

17. Is/was your breathing absolutely normal between attacks ?

18. Do you wheeze on most days or nights ?

19. Are you worse in any one season or another ?

20. If so which season is worse -                      Spring=1, Summer=2  
Autumn=3, Winter=4.

21. Do you wheeze during or after exertion ?

22. If so for how long ?

23. When you get up in the morning how does your chest usually feel ? Is it  
Free  
Tight  
or Very Tight ?

24. If tight or very tight, how long does it usually take to become free ? (hours)

25. Are you ever woken at night with chest tightness, shortness of breath or wheeze ?

Never  
Less than 1/week  
On average 1/week  
2-3 times /week  
most nights

26. Do you wake from sleep with cough ?

27. Do any of the following affect your chest ? (If so indicate in which way).

Shortness of breath   Wheeze   Cough   None

- (a) Going from a warm to a cold room.
- (b) Going into a room where people are or where smoking.
- (c) Traffic fumes.
- (d) Chemicals such as hair spray, perfume or bleach.

Have you ever had:

28. An injury or operation affecting your chest ?

29. Heart trouble ?

30. Bronchitis ?

31. Pneumonia ?

32. Pleurisy ?

33. Pulmonary tuberculosis ?



34. Bronchial asthma ?

35. Hay fever ?

36. Eczema ?

#### SMOKING.

37. Do you smoke ?

If no:-

38. Have you ever smoked as much as one cigarette a day  
(or one cigar a week, or an ounce of tobacco a month)  
for as long as a year ?

If NO to 37 and 38 omit remaining questions on smoking.

39. How old were you when you started smoking regularly ?

40. When did you last give up smoking ?

41. Do (did) you inhale the smoke ?

42. Would you say you inhaled the smoke  
slightly =1  
moderately =2  
deeply =3

43 Do (did) you smoke manufactured cigarettes ?

If yes:-

44. How many do (did) you usually smoke on weekdays ?

45. How many per day at weekends ?

46. Do (did) You smoke plain=1 or filter tip=2 cigarettes ?

47. Do (did) you smoke hand rolled cigarettes ?

48. How much tobacco do (did) you usually smoke per week in this way ?

49. Do (did) you smoke a pipe ?

If yes:-

50. How much pipe tobacco do (did) you smoke per week ?

51. Do (did) you smoke small cigars ?

If yes:-

52. How many of these do (did) you smoke per week ?

53. Do you smoke other cigars ?

If yes:-

54. How many of these do you usually smoke per week ?

## ***APPENDIX II. QUALITY OF LIFE QUESTIONNAIRE.***

### **CHRONIC RESPIRATORY INDEX QUESTIONNAIRE**

First Administration, 7 Point Scale

#### **INTERVIEWER FORM**

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about how short of breath you have been, how tired you have been feeling and how your mood has been.

1. I would like you to think of the activities that you have done during the last 2 weeks that have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life. Please list as many activities as you can that you have done during the last 2 weeks that have made you feel short of breath.

{CIRCLE THE NUMBER ON THE ANSWER SHEET LIT ADJACENT TO EACH ACTIVITY MENTIONED. IF AN ACTIVITY MENTIONED IS NOT ON THE LIST, WRITE IT IN, IN THE RESPONDENT'S OWN WORDS, IN THE SPACE PROVIDED}

Can you think of any other activities you have done during the last 2 weeks that have made you feel short of breath?

[RECORD ADDITIONAL ITEMS]

2. I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 2 weeks. If you haven't done the activity during the last 2 weeks, just answer 'NO'. The activities are:

[READ ITEMS, OMITTING THOSE WHICH RESPONDENT HAS VOLUNTEERED SPONTANEOUSLY. PAUSE AFTER EACH ITEM TO GIVE RESPONDENT A CHANCE TO INDICATE WHETHER HE/SHE HAS BEEN SHORT OF BREATH WHILE PERFORMING THAT ACTIVITY DURING THE LAST WEEK. CIRCLE THE NUMBER ADJACENT TO APPROPRIATE ITEMS ON ANSWER SHEET]

1. BEING ANGRY OR UPSET
2. HAVING A BATH OR SHOWER
3. BENDING

4. CARRYING, SUCH AS CARRYING GROCERIES
5. DRESSING
6. EATING
7. GOING FOR A WALK
8. DOING YOUR HOUSEWORK
9. HURRYING
10. MAKING A BED
11. MOPPING OR SCRUBBING THE FLOOR
12. MOVING FURNITURE
13. PLAYING WITH CHILDREN OR GRANDCHILDREN
14. PLAYING SPORTS
15. REACHING OVER YOUR HEAD
16. RUNNING, SUCH AS FOR BUS
17. SHOPPING
18. WHILE TRYING TO SLEEP
19. TALKING
20. VACUUMING
21. WALKING AROUND YOUR OWN HOME
22. WALKING UPHILL
23. WALKING UPSTAIRS
24. WALKING WITH OTHERS ON LEVEL GROUND
25. PREPARING MEALS

a) Of the items which you have listed, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH ALL ITEMS SPONTANEOUSLY  
VOLUNTEERED AND THOSE FROM THE LIST WHICH  
PATIENT MENTIONED]

Which of these items is most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

(b) Of the remaining items, which is the most important to you in your day-to-day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[READ THROUGH REMAINING ITEMS]

Which of these items is most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

(c) of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

(d) of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

(e) of the remaining items, which is the most important to you in your day-to-day life?

[LIST ITEM ON RESPONSE SHEET]

[FOR ALL SUBSEQUENT QUESTIONS, ENSURE RESPONDENT HAS APPROPRIATE RESPONSE CARD IN FRONT OF THEM BEFORE STARTING QUESTION]

I would now like you to describe how much shortness of breath you have experienced during the last 2 weeks while doing the five most important activities you have selected.

a) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LIST IN 3a] by choosing one of the following options from the card in front of you: [GREEN CARD]

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
- 7 NOT AT ALL SHORT OF BREATH

b) Please indicate how much shortness if breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LIST IN 3b] by choosing one of the following options from the card in from of you: [GREEN CARD]

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
- 7 NOT AT ALL SHORT OF BREATH

c) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LIST IN 3c] by choosing one of the following options from the card in front of you: [GREEN CARD]

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
- 7 NOT AT ALL SHORT OF BREATH

d) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER: INSERT ACTIVITY LISTED IN 3d] by choosing one of the following options from the card in front of you: [GREEN CARD]

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
7. NOT AT ALL SHORT OF BREATH

e) Please indicate how much shortness of breath you have had during the last 2 weeks while [INTERVIEWER; INSERT ACTIVITY LISTED IN 3e] by choosing one of the following options from the card in front of you: [GREEN CARD]

- 1 EXTREMELY SHORT OF BREATH
- 2 VERY SHORT OF BREATH
- 3 QUITE A BIT SHORT OF BREATH
- 4 MODERATE SHORTNESS OF BREATH
- 5 SOME SHORTNESS OF BREATH
- 6 A LITTLE SHORTNESS OF BREATH
7. NOT AT ALL SHORT OF BREATH

5. In general how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

6. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you: (ORANGE CARD)

- 1 EXTREMELY TIRED
- 2 VERY TIRED
- 3 QUITE A BIT OF TIREDNESS
- 4 MODERATELY TIRED
- 5 SOMEWHAT TIRED
- 6 A LITTLE TIRED
- 7 NOT AT ALL TIRED

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME



9. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you. (YELLOW CARD)

- 1 NONE OF THE TIME
- 2 A LITTLE OF THE TIME
- 3 SOME OF THE TIME
- 4 A GOOD BIT OF THE TIME
- 5 MOST OF THE TIME
- 6 ALMOST ALL OF THE TIME
- 7 ALL OF THE TIME

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you: (PINK CARD)

- 1 NO ENERGY
- 2 A LITTLE ENERGY
- 3 SOME ENERGY
- 4 MODERATELY ENERGETIC
- 5 QUITE A BIT OF ENERGY
- 6 VERY ENERGETIC
- 7 FULL OF ENERGY

11. In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks? Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

12. How often during the last 2 weeks did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by choosing one of the following options from the card in front of you: (YELLOW CARD)

- 1 NONE OF THE TIME
- 2 A LITTLE OF THE TIME
- 3 SOME OF THE TIME
- 4 A GOOD BIT OF THE TIME
- 5 MOST OF THE TIME
- 6 ALMOST ALL OF THE TIME
- 7 ALL OF THE TIME

13. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you: (YELLOW CARD)

- 1 NONE OF THE TIME
- 2 A LITTLE OF THE TIME
- 3 SOME OF THE TIME
- 4 A GOOD BIT OF THE TIME
- 5 MOST OF THE TIME
- 6 ALMOST ALL OF THE TIME
- 7 ALL OF THE TIME

14. How often during the last 2 weeks have you felt low in energy? Please indicate how often during the last 2 weeks you have felt low in energy by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps? Please indicate how often during the last 2 weeks you have felt discouraged or down in the dumps by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

16. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

17. How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you: (GRAY CARD)

- 1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
- 2 GENERALLY DISSATISFIED, UNHAPPY
- 3 SOMEWHAT DISSATISFIED, UNHAPPY
- 4 GENERALLY SATISFIED, HAPPY
- 5 HAPPY MOST OF THE TIME
- 6 VERY HAPPY MOST OF THE TIME
- 7 EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED

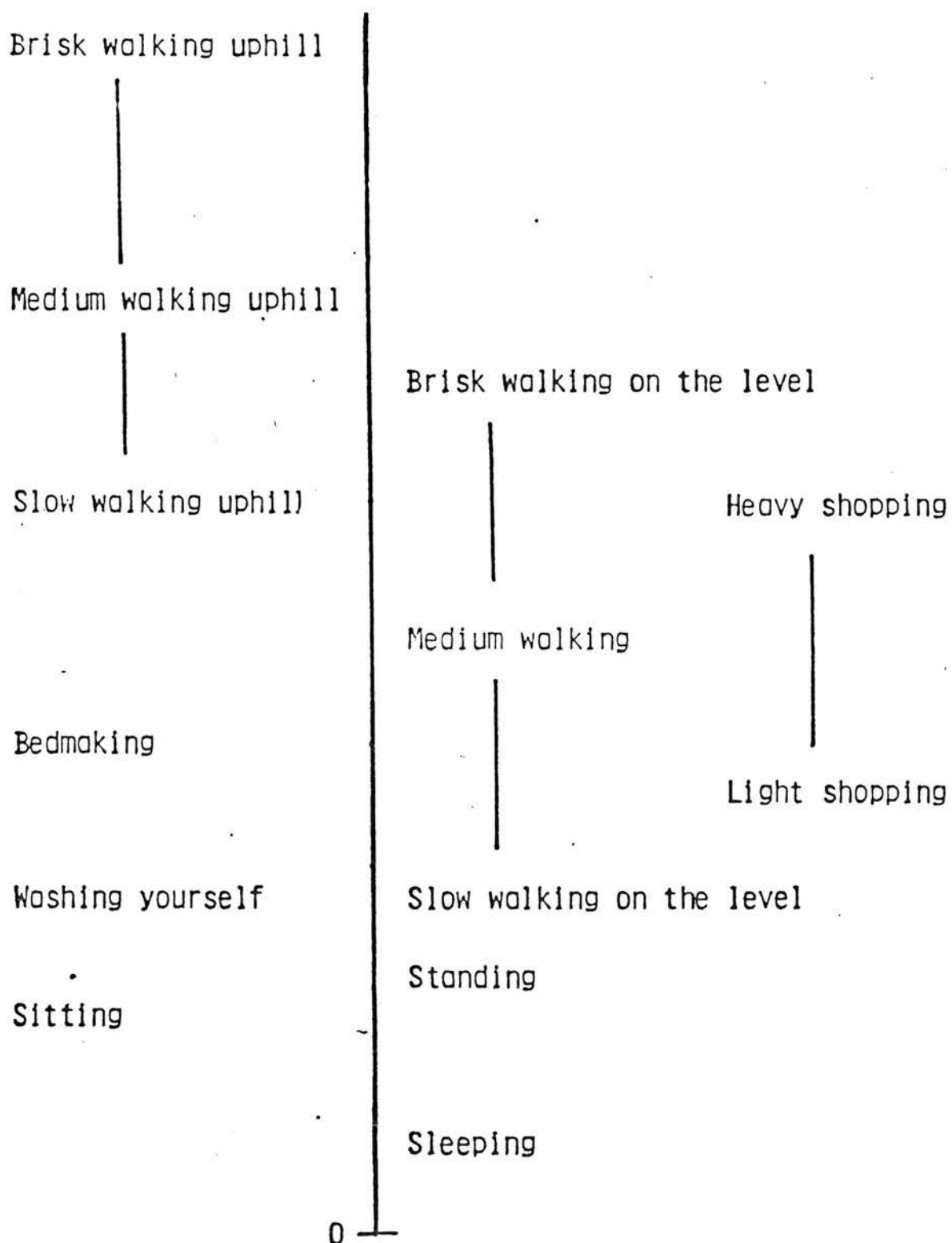
18. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the following options from the card in front of you: (BLUE CARD)

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

19. In general, how often during the last 2 weeks have you felt restless, tense, or uptight? Please indicate how often you have felt restless, tense or uptight by choosing one of the following options from the card in front of you: (BLUE CARD).

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

### APPENDIX III. OXYGEN COST DIAGRAM.



***APPENDIX IV. DIARY CARD.***

### Example

Day Month Year

Date \_\_\_\_\_

[illegible]

## 1. On rising

1. Read before you use your bronchodilators
2. Blow as hard as you can
3. Take 3 readings, and remember the highest 2 readings
4. Are these readings 20 units or less apart?
  - (a) if yes, write the highest in the correct space opposite
  - (b) if no, take more readings until the highest 2 are 20 units or less apart. Write the highest one in the correct space opposite

## 1. On rising

2. 12:00 (mid-day)

3. 16:00 (4 p.m.)

4. 20:00 (8 p.m.)

5. Before be

130	140	155	150	150
-----	-----	-----	-----	-----

## Breathlessness over last 24 hours

Breathlessness over last 24 hours

Record one number between 1 and 7 which represents your breathlessness over the last 24 hours. 1 = Not at all breathless

2  
 ....

1

7 5

7 - The wo

7 - The worst breathlessness I have ever experienced

Sputum Production in last 24 hours

Record one number

- 0 - None  
1 - Only on rising  
2 - All day, less than one eggcupful  
3 - all day, more than one eggcupful

Sputum Colour in last 24 hours

Record one number

- 1 - Clear/white/grey  
2 - Yellow  
3 - Yellowish-green  
4 - Green

### Medicine for Bronchitis

Drug and unit dose

Record the total number of puffs or tablets for each bronchitis.

medicine taken in the last 24 hours

eg if you took 2 puts on 3  
occasions write '6' in the  
correct space

Write '0' if you did not take a particular medicine on any day



## ***APPENDIX V. DETAILS OF PATIENTS WITHDRAWN.***

### **Details of patients withdrawn during the three treatment phases.**

Patient Number.	Treatment.	Reason for withdrawal.
12	Placebo	Cough and wheeze after trial inhalers.
35	Placebo	Pneumonia.
46	Placebo	Failed to attend.
47	Placebo	Infective exacerbation requiring oral steroids
43	Placebo	Infective exacerbation requiring oral steroids
48	Placebo	Abnormal liver function undiagnosed metastatic hepatic disease.
86	Placebo	Infective exacerbation requiring oral steroids
5	BDP 750mcg b.d. + prednisolone	Alopecia, stopped treatment.
8	BDP 750mcg b.d. + prednisolone	Pneumothorax.
37	BDP 1500mcg b.d. + prednisolone	Diabetes mellitus.
42	BDP 750mcg b.d. + prednisolone	Infective exacerbation requiring oral steroids.
73	BDP 750mcg b.d. + placebo	Did not attend, severe depression.
99	BDP 1500mcg b.d. + placebo	Infective exacerbation requiring oral steroids

***APPENDIX VI. REPRINT OF REFERENCE 95.***

Weir DC, Gove RI, Robertson AS, Burge PS. Corticosteroid trials in non-asthmatic chronic airflow obstruction; a comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax* 1990;45:112-117.

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## Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate

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# Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate

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## Abstract

One hundred and twenty seven adults considered on clinical grounds to have non-asthmatic chronic airflow obstruction entered a randomised, double blind, placebo controlled, crossover trial comparing the physiological response to inhaled beclomethasone dipropionate 500  $\mu$ g thrice daily with oral prednisolone 40 mg a day, both given for two weeks. One hundred and seven patients completed the study. Response was assessed as change in FEV<sub>1</sub> and FVC measured on the last treatment day, and as change in mean peak expiratory flow (PEF) over the final seven days of treatment from home PEF recordings performed five times daily. A full response to treatment was defined as an increase in FEV or FVC, or an increase in mean daily PEF over the final seven days of treatment, of at least 20% from baseline values. An improvement in one measurement of at least 15%, or of 10% in any two measurements, was defined as a partial treatment response. Response to placebo showed a significant order effect, suggesting a carry over effect of active treatment of at least three weeks. Response to active treatment was therefore related to initial baseline values, and compared with placebo by considering responses in the first treatment phase only. A full response to oral prednisolone (16/38) was significantly more common than to placebo (3/35). The number of full responses to inhaled beclomethasone (8/34) did not differ significantly from the number responding to oral prednisolone or placebo in the first treatment phase, though full and partial responses to inhaled beclomethasone (12/34) were significantly more common than those to placebo (4/35). When all three treatment phases were considered 44/107 patients showed a full response to one or both forms of corticosteroid treatment, a response to prednisolone (39) occurring more frequently than to inhaled beclomethasone (26). Only 21 of the 44 responders showed a response to both forms of treatment. Inhaled beclomethasone dipropionate 500  $\mu$ g thrice daily was inferior to oral prednisolone 40 mg per day, but better than placebo, in producing improvement in physiological measure-

ments in patients thought to have non-asthmatic chronic airflow obstruction. It was, however, an effective alternative in over half of those showing a response to prednisolone.

Oral corticosteroids improve symptoms and lung function in some patients with severe chronic airflow obstruction related to cigarette smoking.<sup>1</sup> Published trials have in general used doses of oral medication which in the long term would have serious systemic side effects.<sup>2-4</sup> The efficacy of inhaled corticosteroids in asthma is well established but only two previous studies have looked at the effect of this form of treatment in patients with chronic airflow obstruction, both with small numbers of patients.<sup>5,6</sup> The study of Harding and Freedman identified a response to 400  $\mu$ g/day of inhaled betamethasone valerate in only three of six patients who showed a response to oral prednisolone. All responders to the inhaled drug were inpatients and the authors suggest that this may have improved compliance and delivery of the drug to the airways. In the recent study of Wardman *et al* with 22 outpatients, however, all with good inhaler technique, the five responders to oral prednisolone improved to the same degree after two weeks' treatment with inhaled beclomethasone dipropionate 1500  $\mu$ g per day. The different results may reflect different doses and delivery of the drug to the airways, but the role of inhaled corticosteroids in patients with severe chronic airflow obstruction is still unclear.

The aim of this study was to compare the response to oral prednisolone 40 mg/day with that to inhaled beclomethasone dipropionate 500  $\mu$ g thrice daily in outpatients with non-asthmatic chronic airflow obstruction.

## Methods

### SUBJECTS

Outpatients with adult onset chronic airflow obstruction of at least five years' duration and an FEV<sub>1</sub> below 70% predicted were recruited to the trial. Patients were excluded if they had a clinical diagnosis of asthma, respiratory symptoms in childhood, variability in symptoms except in association with infections, acute attacks of wheezing and

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breathlessness, or deterioration after exposure to specific allergens. A lack of a "fixed" element in the airflow obstruction after inhalation of bronchodilator also favoured asthma as the diagnosis. The presence of some reversibility of airflow obstruction in response to inhaled bronchodilators was deliberately not chosen as an exclusion criterion so that its effect on steroid response could be assessed. No patient had received oral or inhaled corticosteroids in the preceding six months. All patients gave informed consent.

#### MEASUREMENTS

Spirometric indices were determined on two occasions during the baseline phase before any treatment was given, and on the final day of each treatment period. Patients were asked to refrain from inhaled bronchodilators for six hours before the measurements, and visits were performed at the same time of day. FEV<sub>1</sub> and FVC were measured on a dry bellows spirometer (Vitalograph), the mean of three technically satisfactory attempts within 10% or 100 ml (whichever was the smaller) being used for subsequent analysis. Baseline FEV<sub>1</sub> and FVC were taken as the highest mean measurements recorded on the two baseline visits before any treatment.

Lung volumes and single breath carbon monoxide gas transfer (TLCO) were determined once during the baseline period and at the end of each treatment phase. A closed circuit helium dilution technique was used to measure lung volume subdivisions, rebreathing being continued until the concentration of helium was stable or for a maximum of 20 minutes. Single breath TLCO was taken as the mean of two satisfactory manoeuvres within 15% of each other.

Airflow reversibility in response to salbutamol and ipratropium bromide was determined during the baseline period. Two doses of salbutamol (200 µg and 10 mg) were administered sequentially, and the response was determined 20 minutes after each dose. On a subsequent day 72 and 500 µg of ipratropium bromide were given and the spirometric response was assessed 25 minutes after each dose. The smaller dose of each drug was given by a metered dose inhaler and the larger dose by an Inspiron mini-Neb nebuliser, the drug being nebulised to dryness. Bronchial responsiveness to inhaled histamine was determined by the method of Cockcroft *et al.*,<sup>7</sup> on the second baseline visit if the FEV<sub>1</sub> was above 0.6 l.

After the second baseline visit patients were asked to measure peak expiratory flow rate (with a mini Wright's peak flow meter) four hourly during waking hours at home, and record the best of at least three attempts with the best two within 20 l/min. All baseline values were obtained during the two weeks before the first treatment phase and mean daily PEF was calculated over the final seven days of this period. Diurnal variation in PEF was calculated from the same readings as mean daily maximum PEF (mean daily maximum PEF minus mean daily minimum PEF divided by mean daily PEF).

Serum IgE concentrations were measured by a PRIST technique and skinprick tests performed with house dust, *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, cat fur, and a control solution, a positive result being defined as a weal 2 mm greater than that obtained with the control solution in two or more tests.

Inhaler technique was checked at each visit and corrected as necessary. All patients continued their usual bronchodilator treatment unchanged during the trial, and were instructed to maintain a constant timing between doses and PEF readings.

#### DESIGN

The trial was a randomised, double blind, double dummy, crossover study designed to compare inhaled beclomethasone dipropionate 500 µg thrice daily, oral prednisolone 40 mg/day, and placebo. Each treatment was given for two weeks followed by a two week washout period before the next treatment period. The first treatment period was preceded by a four week baseline period. Patients attended the laboratory on days 1 and 14 of the baseline period for initial investigations, and on the last day of each treatment period for subsequent assessments.

#### ANALYSIS

A full response to treatment was defined as an improvement in absolute values of FEV<sub>1</sub> or FVC on the final treatment day, or mean PEF over the last seven days of treatment, of at least 20% when compared with baseline. An improvement of at least 15% in any one measure or at least 10% in any two measures was defined as a partial treatment response.

Baseline data were compared by means of a paired or unpaired Student's *t* test for normally distributed data or a Wilcoxon signed rank or rank sum test for data not normally distributed. Treatment order effect was assessed by a logit regression on proportions, the GLIM statistical package being used.<sup>8</sup> Active treatment response rates were compared by McNemar's test, and the responses to the treatments given during the first phase by a  $\chi^2$  test.

All predicted values are derived from published equations.<sup>9</sup>

#### Results

Of the 127 patients who entered the study, 107 completed the protocol. Eleven patients defaulted at subsequent visits: six had an infective exacerbation of their disease, one died of an unrelated cause during the run in period, and two had complications during the oral prednisolone phase (exacerbation of chronic duodenal ulceration in one, left ventricular failure in the other). The mean age (63 years) and the FEV<sub>1</sub> and FVC (39% and 70% predicted) of those withdrawn were similar to the mean values in patients who completed the study. The baseline lung function characteristics of the study group are given in table 1 and details of smoking and atopy in table 2.

There was a significant order effect in the

Table 1 Baseline lung function characteristics of the study group (mean (SD) values unless otherwise indicated)

(25F) Number	107 (25F)
Age: years	62.9 (9.0)
FEV <sub>1</sub> : litres	1.19 (0.47)
$\bar{v}_0$ predicted	44.2 (16.7)
Forced vital capacity: $\bar{v}_0$ predicted	79.2 (19.0)
Peak flow (PEF): $\bar{v}_0$ predicted	52.4 (17.9)
Total lung capacity: $\bar{v}_0$ predicted	121.5 (19.4)
Residual volume: $\bar{v}_0$ predicted	173.6 (52.0)
Transfer coefficient: $\bar{v}_0$ predicted	77.8 (31.7)
Diurnal variation in PEF: $\bar{v}_0$ mean	19.8 (9.9)
PC <sub>20</sub> (mg/ml): geometric mean (range)	0.81 (0.03–16.0)
FEV <sub>1</sub> : indices of reversibility of airflow obstruction	
As $\bar{v}_0$ initial FEV <sub>1</sub> , in response to:	
10 mg salbutamol	18.0 (15.9)
200 µg salbutamol	11.4 (11.2)
500 µg ipratropium bromide	20.1 (17.0)
72 µg ipratropium bromide	13.1 (11.7)
As $\bar{v}_0$ (predicted minus initial) FEV <sub>1</sub> , in response to:	
10 mg salbutamol	15.5 (16.8)
200 µg salbutamol	10.9 (13.7)
500 µg ipratropium bromide	19.2 (26.1)
72 µg ipratropium bromide	12.5 (16.4)
PC <sub>20</sub> —provocative concentration of histamine causing a 20% fall in FEV <sub>1</sub> .	

Table 2 Smoking and atopy in the 107 subjects

Number of:	
Current smokers	41
Ex-smokers	54
Lifelong non-smokers	12
Mean (SD) cigarette consumption (cigarette years)	761 (547)
Number with chronic bronchitis*	77
Serum IgE (kU/l): geometric mean (range)	74 (3–4500)
Number with positive skin test responses	46

\*Medical Research Council definition.

response to placebo, in that the placebo response rate was greater when placebo had been preceded by active treatment ( $\chi^2_1 = 5.06$ ,  $p < 0.05$ ; table 3); this was not seen with the response to prednisolone or to beclomethasone dipropionate ( $\chi^2_1 = 0.75$  and  $\chi^2_1 = 0.02$ ). Because of this order effect, response to treatment was defined with respect to initial baseline values before any trial treatment had been given, and the two active treatments were compared with placebo by a parallel group analysis of the first treatment phase data.

#### ANALYSIS OF DATA AS A PARALLEL GROUP STUDY USING THE FIRST TREATMENT PHASE ONLY

On entry into the study patients randomised to receive placebo, beclomethasone, or prednisolone for the initial treatment phase, did not differ in terms of baseline physiological characteristics (table 4). The number of patients showing a full response to prednisolone (16/38)

Table 3 Number of full responders (partial responders in parentheses) to each treatment according to the phase in which it was administered

	Phase 1	Phase 2	Phase 3
Placebo	3 (1)/35	7 (1)/31	12 (0)/41**
Beclomethasone	8 (4)/34	10 (4)/41	8 (2)/32
Prednisolone	16 (1)/38	12 (1)/35	11 (3)/34

\*\* $p < 0.05$  for treatment order effect.

was significantly greater than the number showing a similar response to placebo (3/35,  $\chi^2_1 = 10.64$ ;  $p < 0.005$ ). A full response occurred more frequently with beclomethasone (8/34) than with placebo, though this was not significant ( $\chi^2_1 = 2.22$ ; NS). When partial responses are included in the analysis the response rate for both inhaled beclomethasone (12/34) and oral prednisolone (17/38) was significantly greater than that for placebo (4/35:  $\chi^2_1 = 5.51$ ,  $p < 0.02$ ; and  $\chi^2_1 = 9.86$ ,  $p < 0.002$  respectively). There was no significant difference in the response to either active drug in this analysis either for full responders ( $\chi^2_1 = 2.79$ ,  $p < 0.1$ ) or when full and partial responders were considered ( $\chi^2_1 = 0.67$ ).

#### ANALYSIS OF DATA FROM ALL THREE TREATMENT PHASES IN THE CROSSOVER STUDY

When all three treatment phases were considered to allow within subject comparison of response, 21 patients showed a full response to both prednisolone and beclomethasone. A further 18 patients responded to prednisolone only and five to beclomethasone only. Six of the 18 prednisolone only responders showed a partial response to beclomethasone and one of the five beclomethasone only responders showed a partial response to oral prednisolone. In total, 44/107 (41%) patients showed a full response to prednisolone or beclomethasone and a further six a partial response. The response rate was significantly greater with prednisolone than beclomethasone (Mcneemar's test 2.71,  $p < 0.05$ ).

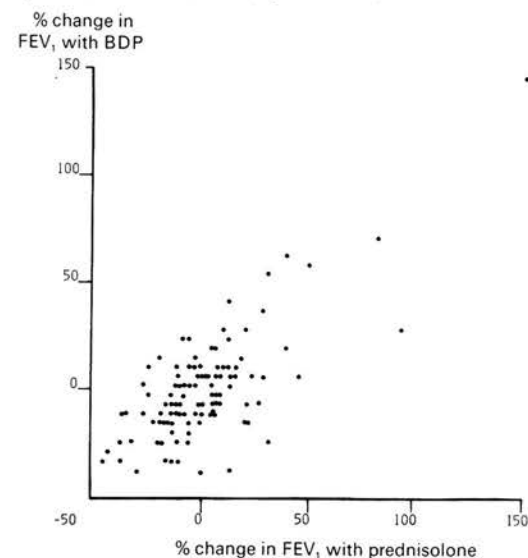


Figure 1 Percentage change in FEV<sub>1</sub> from baseline values in individual patients after treatment with prednisolone and beclomethasone (BDP). Slope of least squares regression line = 0.72 (SE 0.06).

Table 4 Baseline characteristics of the groups according to the treatment received in the first phase (mean (SD) unless otherwise indicated)

	Placebo	Beclomethasone	Prednisolone
Number	35 (7F)	34 (11F)	38 (7F)
Age: years	64.2 (8.1)	60.8 (10.1)	63.7 (8.5)
FEV <sub>1</sub> : litres	1.15 (0.48)	1.21 (0.53)	1.20 (0.43)
$\bar{v}_0$ predicted	42.8 (14.2)	45.1 (18.2)	44.7 (17.7)
Reversibility of airflow obstruction (as $\bar{v}_0$ baseline) in response to:			
10 mg salbutamol	16.3 (18.3)	20.2 (16.3)	17.7 (13.3)
500 µg ipratropium bromide	20.0 (18.5)	22.6 (19.5)	18.0 (12.9)
Cigarette consumption:			
Cigarette years	712 (522)	620 (486)	896 (566)
Number of:			
Current smokers	11	10	7
Ex-smokers	19	20	28
Lifelong non-smokers	5	4	3

There are no significant differences between groups.



Figure 2 Percentage change in mean daily peak expiratory flow (PEF) from baseline value in individual patients after treatment with prednisolone and beclomethasone (BDP). Slope of least squares regression line = 0.46 (SE 0.05).

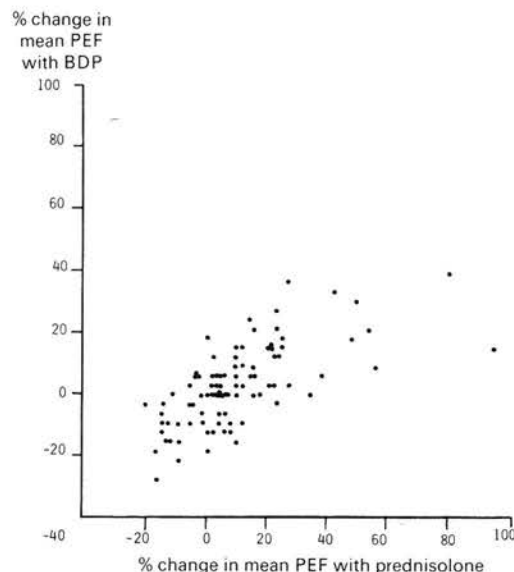


Figure 3 Percentage change in forced vital capacity (FVC) from baseline value in individual patients after treatment with prednisolone and beclomethasone (BDP). Slope of least squares regression line = 0.62 (SE 0.07).

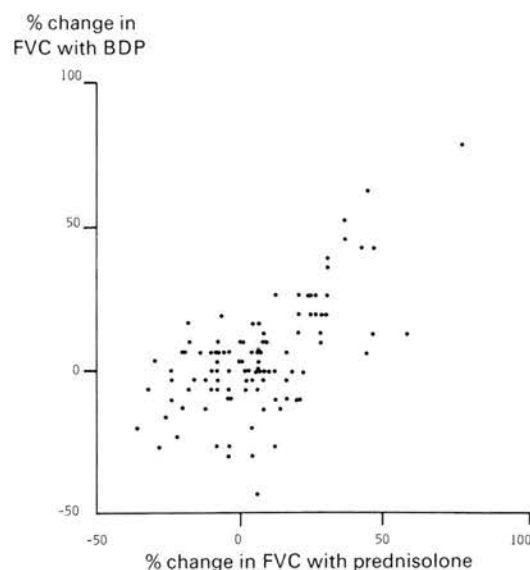
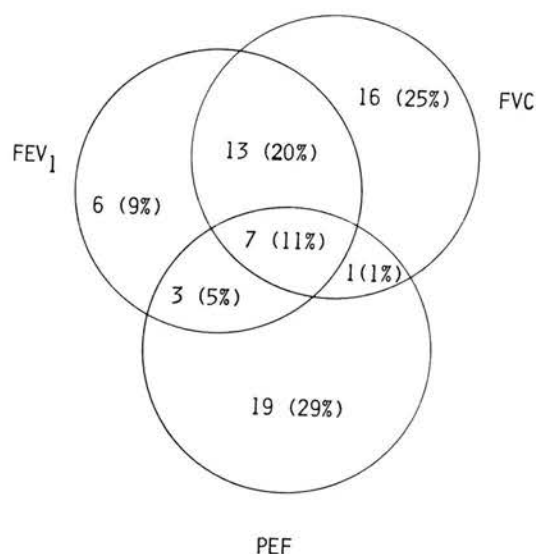


Figure 4 Venn diagram showing the measurements in which response occurred in the 65 individual responses to treatment.



The responses of individual patients to oral prednisolone and inhaled beclomethasone are shown in figures 1–3 for FEV<sub>1</sub>, FVC, and PEF. The slope of the least squares regression line for each plot is significantly different from the line of identity, indicating a greater effect of prednisolone on each measurement.

A full response to an active treatment occurred on 65 occasions. The measurements in which a response was seen on these occasions are shown in the Venn diagram (fig 4). A full response was seen in all three measurements on only seven occasions and in two of the measurements on a further 17 occasions; in most cases (41) a full response was seen in only one measurement.

In the 44 patients who had a full response to prednisolone or beclomethasone the change in the measurement showing the greatest response was expressed as a percentage of the patient's predicted value, a measure independent of baseline FEV<sub>1</sub> (fig 5). The responders remained distinct from the non-responders.

The mean reversibility in FEV<sub>1</sub> in response to 10 mg inhaled salbutamol was 18%, expressed as a percentage of the prebronchodilator value (table 1). If expressed in terms of potential reversibility—that is, as a percentage of the predicted minus the prebronchodilator value—the mean improvement was 15.5%. Only 13 patients showed an increase in this measurement of over 50%, indicating that most of the patients had relatively fixed airflow obstruction. Response to prednisolone or beclomethasone or both in the 13 “reversible” patients (4/13) was similar to that seen in the “irreversible” patients (40/94;  $\chi^2_1 = 0.64$  NS).

Cigarette consumption in the patients varied from zero to 2520 cigarette years, with a mean of 761 cigarette years (table 2). Twelve patients claimed to be life long non-smokers. Eighty one patients admitted to a cigarette consumption in excess of 400 cigarette years. Full and partial responses to prednisolone or beclomethasone or both were similar in this group of heavier smokers (39/81) and in the remaining patients (11/26;  $\chi^2_1 = 0.57$ ; NS).

## Discussion

The finding of a significant order effect with placebo treatment complicated the analysis of the data from this trial. The analysis of the data on the first treatment phase removes the confounding influence of the order effect and shows that both active treatments are superior to placebo in producing a physiological response in these patients. In this analysis oral prednisolone produced a response in more subjects than inhaled beclomethasone, though the difference was not significant. Previous studies have not always commented on an order effect, though some have used a single blind design that would avoid this problem.<sup>3,6</sup> Two smaller studies with a crossover design found no treatment order effect,<sup>10,11</sup> possibly because of the smaller numbers of patients.

Although in our study the order effect was seen only with placebo it might have occurred to some extent with active treatment. The lack



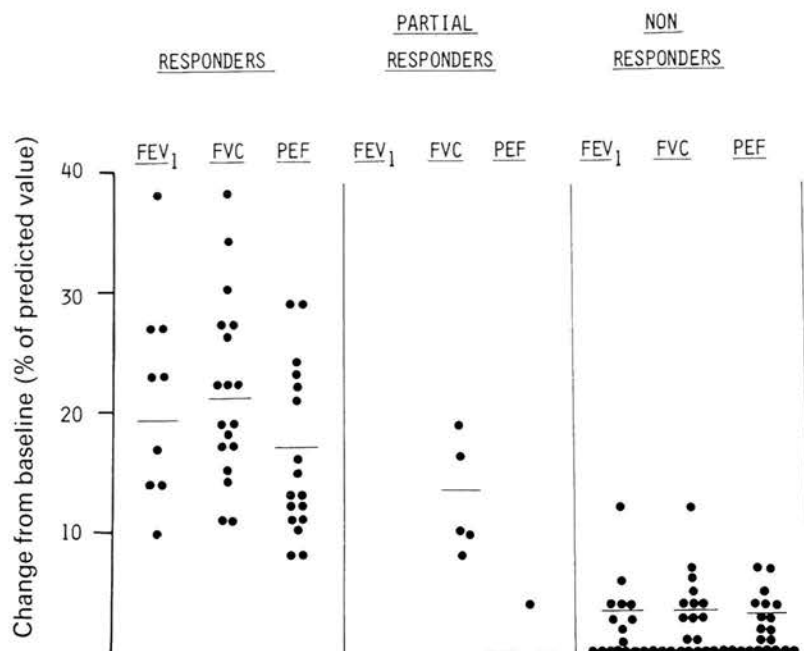


Figure 5 Change from baseline after treatment in the measurement that showed the greatest percentage change. The change is expressed as a percentage of the predicted value for the patient for that measurement. The horizontal lines represent the mean response of all the patients who showed a positive change.

of any detectable order effect for the response to prednisolone and beclomethasone suggests that the action of the second active treatment is more powerful than the carry over effect of the initial treatment. We feel justified therefore in using data from all three treatment phases to further compare individual responses to prednisolone and beclomethasone. When this was done prednisolone was superior to beclomethasone in producing a response, though over half of the patients showing a response to prednisolone also responded to inhaled beclomethasone. The reason why five patients responded to inhaled beclomethasone only is not clear.

Our study may be criticised for the response criteria adopted. Response was expressed in terms of percentage change from the baseline value, a criterion used in previous trials.<sup>6 10 11 13</sup> The validity of such a definition is questionable when the absolute value of the variable studied is low. In these circumstances small changes that are within the error of measurement of the variable may assume undue significance. Only 4% of our responders, however, showed a change in FEV<sub>1</sub> or FVC that was within the 95% confidence limits for short term variability in FEV<sub>1</sub> and FVC published recently.<sup>14</sup> Previous studies of longer term variability in spirometric indices in similar patients suggest that our criteria are reasonable.<sup>15 16</sup> Expressing change as a percentage of a measure independent of the baseline—that is, the predicted value—did not suggest that any responders had been misclassified (fig 5). One partial responder and two non-responders may have been wrongly classified.

Symptomatic change was not determined formally in all patients. Visual analogue scales for five symptoms and six minute walking distances were, however, determined in the first 83 patients recruited to the trial.<sup>17</sup> Six

minute walking distances improved significantly with both active treatments in the steroid responsive patients, whereas no effect was seen with treatment in the non-responders. Visual analogue scores showed a wide variation and, although they improved in all response groups with treatment, the changes were not significant.

A further possible criticism of our results is that because of the "soft" entry criteria we inadvertently included patients with missed asthma in the study population. The criteria were chosen to reflect clinical practice and only where the physician was unsure of the benefit of steroid treatment—that is, where asthma was not present—was a patient entered. Those who had had respiratory disease in childhood were excluded, which eliminated many patients with asthma. Not all patients were current smokers or ex-smokers, although most had smoked heavily. Many patients showed a degree of reversibility in response to inhaled bronchodilators that was within the "asthmatic" range of 20% or more of the prebronchodilator FEV<sub>1</sub>. This, however, is a misleading measure of reversibility in patients with a low prebronchodilator FEV<sub>1</sub>. A better indication of reversibility is obtained by considering the reversibility as a percentage of the predicted FEV<sub>1</sub> minus the prebronchodilator value (table 1). Most of our patients had largely irreversible airflow obstruction. Response to one or both corticosteroid treatments was not related to past cigarette consumption or to reversibility in response to inhaled salbutamol, suggesting that our patients were predominantly non-asthmatic. The degree of response to corticosteroids shown in figure 5 shows a unimodal distribution, again suggesting that the patients came from a single disease group. Hence we believe that most of the patients were not asthmatic, and that our findings are relevant to patients diagnosed as having chronic airflow obstruction in clinical practice.

The trial of Wardman *et al*<sup>6</sup> showed that 1500 µg beclomethasone/day was comparable to oral prednisolone 30 mg in patients similar to ours, in terms both of the number showing a response and of the degree of improvement seen in the measure of lung function. Like Harding and Freedman,<sup>5</sup> we have not found this to be the case. The likeliest explanation for this is differences in selection of patients and perhaps in deposition of aerosol in the lung. We attempted to optimise inhaler technique in our group by checking and correcting technique at each visit, but possibly improved delivery of the drug to the airways by means of a spacing device would have produced more responders to beclomethasone. Our results would suggest, however, that inhaled beclomethasone 500 µg thrice daily should be considered an effective treatment in over half of patients with non-asthmatic airflow obstruction who show a response to oral prednisolone 40 mg daily.

The contribution of the following is gratefully acknowledged: Dr D Geddes for help with the trial design, Allen and Hanburys Ltd for financial support and providing the inhalers,

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